Neurophysiological and Neuropsychological Aspects of Time Processing in Children and Adults with and without ADHD

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Summary

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common mental disorders of children and adolescents, and a sizable number of ADHD patients continue to be impaired in later life. Developmental changes of cardinal symptoms of ADHD and their possible overlap with other deficits as well as influences of compensatory mechanisms in adult age make direct comparisons of children and adults with ADHD difficult.

In this work, neurophysiological and neuropsychological markers of ADHD are investigated in order to better compare different attention aspects of children and adults with ADHD.

A central aim of this piece of work was to compare childrens' and adults' performances on different tasks, exploring either classical executive functions like inhibition and attention, or probing more basal functions like alertness and temporal processing. The main focus was on aspects of temporal processing, though.

In **study A**, event-related potentials (CNV and Nogo P300) during cued continuous performance tasks were used to compare ADHD-related temporal processing (CNV) and response inhibition (Nogo P300) deficits in children (32 with ADHD, mean age 11.2 years, and 31 controls, mean age 11.1 years) and adults (22 with ADHD, mean age 42.7 years, and 22 controls, mean age 44.0 years).

In **study B**, children and adults with ADHD were compared to controls on two time processing tasks containing time reproduction (in the seconds time range) and time discrimination (in the milliseconds time range).

Developmental as well as ADHD-related effects could be found in both studies.

The results show that there exist differences between both children and adults with ADHD compared to their matched controls. However, the pattern of differences is not the same for children and adults. This leads to the conclusion that ADHD- related deficits concerning temporal processing and inhibition persist into adulthood despite alterations of their qualitative aspects during development.

Zusammenfassung

Die Aufmerksamkeits- und Hyperaktivitätsstörung (ADHS) ist eine der häufigsten psychischen Erkrankungen im Kindes- und Jugendalter. Viele Betroffene sind auch im Erwachsenenalter beeinträchtigt. Entwicklungsbedingte Veränderungen der Hauptsymptome, ihre mögliche Überlappung mit anderen Defiziten sowie Einflüsse von Kompensationsmechanismen im Erwachsenenalter erschweren den direkten Vergleich zwischen Kindern und Erwachsenen mit ADHS.

Um verschiedene Aufmerksamkeit-bezogene Aspekte zwischen betroffenen Kindern und Erwachsenen besser vergleichen zu können, wurden hier neurophysiologische und neuropsychologische ADHS-Marker untersucht.

Eines der zentralen Ziele dieser Arbeit war es, die Leistungen der Kinder und Erwachsenen in verschiedenen Aufgaben hinsichtlich klassischer Exekutivfunktionen wie Inhibition und Aufmerksamkeit zum einen und grundlegender Funktionen wie Alertness und Zeitverarbeitung zum anderen zu vergleichen. Der Schwerpunkt wurde dabei auf Aspekte der Zeitverarbeitung gelegt.

In **Studie A** wurden Ereignis-bezogene Potentiale (CNV und Nogo P300) während eines Daueraufmerksamkeitstests erhoben, um somit ADHS-bezogene Defizite in der Zeitverarbeitung (CNV) und Antwortinhibition (Nogo P300) zwischen Kindern (32 mit ADHS, Durchschnittsalter [DA] 11.2 Jahre und 31 Kontrollkindern ohne ADHS, DA 11.1 Jahre) und Erwachsenen (22 mit ADHS, DA 42.7 Jahre und 22 Kontrollerwachsene ohne ADHS, DA 44.0 Jahre) zu vergleichen.

In **Studie B** erfolgte der Vergleich der betroffenen Kinder und Erwachsenen mit den Kontrollen bezüglich zweier verschiedener Zeitverarbeitungsaufgaben: einer Reproduktionsaufgabe im Sekundenbereich und einer Diskriminationsaufgabe im Millisekundenbereich.

Die Resultate beider Studien zeigen, dass sich sowohl Kinder als auch Erwachsene mit ADHS von ihren jeweiligen Vergleichsgruppen unterscheiden. Das Muster der Unterschiede ist jedoch bei Kindern anders als bei Erwachsenen. Dies führt zur Hypothese, dass ADHS-bezogene Defizite bezüglich Zeitverarbeitung und Inhibition bis ins Erwachsenenalter erhalten bleiben, dass sie sich in ihren qualitativen Aspekten aber über die Entwicklung hinweg verändern.

1 General Introduction

1.1 Core Symptoms and Aetiological Theories of ADHD

Attention Deficit/Hyperactivity Disorder is an early onset syndrome, characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity. It is one of the most frequently diagnosed childhood psychiatric disorders, with an estimated prevalence of 3% to 7% among school-age children (American Psychiatric Association [APA], 1994). In many affected individuals, impairment persists into adolescence and adulthood, but the behavioural core symptoms improve throughout development and at least partially recover or change their nature, so that some individuals no longer meet criteria for the disorder (Biederman, Mick, & Faraone, 2000). For instance, hyperactivity-impulsivity is most prominent during younger age stages, whereas in adolescents and adults, inattention and related dysfunctions replace hyperactivity-impulsivity (Hart, Lahey, Loeber, Applegate, & Frick, 1995).

Traditional theories implicate impaired executive functions, mainly inhibitory processes, mediated by neural circuits in the prefrontal cortex and striatum as causing ADHD (Barkley, 1997; Castellanos, 2001). These theories have been more and more complemented by theories that recognized the behavioural and neurocognitive heterogeneity of ADHD by integrating also non-executive function deficits such as motivational (Sonuga-Barke, 2003) and state regulating (Sergeant, 2000; van der Meere, 2005) factors, suggesting multimodal pathways of ADHD and emphasizing the dynamic interplay of frontal-cortex-functions and noncortical neural functions in the cause, time-course and remission of core deficits related to ADHD (Halperin & Schulz, 2006; Sagvolden, Johansen, Aase, & Russell, 2005; Sergeant, 2000; Sonuga-Barke, 2003). Leading theories include aspects of attention, executive functions, state regulation and motivation and temporal information processing. Some neuroimaging studies have indicated involvement of processes involving subcortical-thalamocortical neuroal loops, along with cerebellar-frontal networks (Giedd, Blumenthal, Molloy, & Castellanos, 2001; Swanson, 2002a).

One special theory proposes a “dual-process” model of ADHD claiming that disturbances in basal ganglia- and /or cerebellar-thalamo-cortical loops underlie the behaviour-

ally observable deficits in executive functions. They make a distinction between bottom-up driven factors like activation, arousal, alerting, motivation, reward and temporal processing as being involved in the aetiology of ADHD and top-down cognitive control processes mediated by prefrontal cortex as being involved rather in the remission of ADHD symptoms (Halperin & Schulz, 2006; Halperin, Trampush, Miller, Marks, & Newcorn, 2008; King, Colla, Brass, Heuser, & von Cramon, 2007). Furthermore, they postulate that a subcortical neural dysfunction causes ADHD, which is present early in ontogeny and remains relatively stable throughout life. Prefrontally mediated executive functions, on the other hand, emerge during later childhood and adolescence and are associated with the reduction of symptoms typically seen over development by compensating for the primary and enduring subcortical deficits (Halperin et al., 2008). Thus, according to Halperin et al. (2006) the prefrontal cortex is not associated with the cause of the disorder, although it is intimately involved in the manifestation of ADHD symptoms (Barkley, 1997; Himelstein, Newcorn, & Halperin, 2000; Swanson, 2002b). This is especially interesting when it comes to the discussion of adult ADHD and the comparison of ADHD-related symptoms between children and adults. How can stable core symptoms be differentiated from transient developmental lags and from similar symptoms caused by different neural dysfunctions? And how do these different processes relate to one another, how do they merge and influence one another during development? In contrast to adults, most children with early frontal lobe damage do not show symptoms of ADHD (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Eslinger, Grattan, Damasio, & Damasio, 1992). Furthermore, some authors claim that if dysfunction of the prefrontal cortex and of executive functions were the primary determinants of ADHD, behavioural difficulties should generally not manifest until relatively late in development considering the late maturation of frontal functions (Anderson et al., 1999; Eslinger et al., 1992; Goldman, 1971). However, symptoms of ADHD would almost always be evident during the preschool years (Barkley, Fischer, Edelbrock, & Smallish, 1990) and the severity of core symptoms would tend to diminish with age (Biederman et al., 2000; Hill & Schoener, 1996). Thus, the developmental trajectory of the prefrontal cortex and executive functions would be inconsistent with the typical emergence and developmental trajectory of ADHD, but rather would parallel the diminution of core symptoms commonly seen in children with ADHD (Biederman et al., 2000; Hill & Schoener, 1996). Only a small subgroup meeting ADHD criteria which is described as having a later age of

onset (Applegate et al., 1997; Hesslinger, Tebartz van Elst, Mochan, & Ebert, 2003), could possibly be better accounted for by the prefrontal hypothesis of ADHD.

The late development of the prefrontal cortex and its close connection to the also relatively late development of executive functions makes it an ideal brain region to develop top-down compensatory cognitive and neural mechanisms, able to hide more diffuse cognitive deficits (Halperin & Schulz, 2006). Consistent with this suggestion is a neuroimaging study whose results suggest that ADHD symptomatology in children is partly caused by anomalies of frontal-lobe maturation (Rubia et al., 2000), which lose importance in adulthood (Schoechlin & Engel, 2005). Of course, this compensation of prefrontal cortex functions throughout development varies depending on other intrinsic (neurobiological) and extrinsic (environmental influences) factors. This "subcortical deficit / cortical compensation" theory leads to the assumption that tests requiring high levels of effort and conscious control should seldom produce differences in the performance from controls and adolescents or adults who had childhood ADHD; rather, tests that involve less conscious control processes like reaction time or reaction time variability should more clearly differentiate those with and without childhood ADHD irrespective of adult current status (Halperin & Schulz, 2006). Are executive functions and frontal brain areas really associated only secondary to ADHD without playing a core role in the development of the disease? Other developmental and brain imaging studies (Castellanos et al., 2002; Durston, 2003) and results found here put this statement into question (see discussion).

1.2 Neurobiological Theories of Time Processing and ADHD

A main focus in this thesis is on temporal processing as this is considered to be strongly connected with attentional functions (Macar et al., 2002), and because deficits in temporal processing found in ADHD subjects ranging from children to adults (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Barkley, Koplowitz, Anderson, & McMurray, 1997; Barkley, Murphy, & Bush, 2001; McInerney & Kerns, 2003; Sonuga-Barke, Saxton, & Hall, 1998) make it a promising endophenotype (as discussed below, Castellanos & Tannock, 2002). There is agreement on the existence of two distinct systems of temporal processing: a more "automatic" system for timing in the milliseconds range which is also considered important for motor coordination and computed by the cerebellum and basal gan-

glia (Harrington, Haaland, & Hermanowicz, 1998) is differentiated from a more "cognitive" system for timing in the seconds to minutes range which is supposed to be important for temporal estimation and reproduction and computed by frontal-striatal circuits (Karmarkar & Buonomano, 2007; Lewis & Miall, 2003a, 2003b, 2006; Madison, 2001). Thus, temporal processing in the range of less than 1 sec. duration should not primarily depend on working memory and attentional allocation abilities nor on motivational aspects, in contrast to temporal processing of time intervals longer than 1 second (Mangels, Ivry, & Shimizu, 1998). So far, impairments of either system are compatible with experimental findings in ADHD and supported by neurobiological models as well as by imagery studies (for reviews see (Durston, de Zeeuw, & Staal, 2009; Giedd et al., 2001; Kelly, Margulies, & Castellanos, 2007; Kieling, Goncalves, Tannock, & Castellanos, 2008; Willis & Weiler, 2005). In a recent study, Himpel et al. (2009) suggested time discrimination within the milliseconds range as an endophenotype for ADHD (Himpel et al., 2009).

1.3 Neuropsychology and Time Processing in ADHD

According to Barkley (Barkley, 1997), impaired time perception in ADHD subjects is a consequence of inhibition and executive deficits observed in these subjects. Especially the reproduction of time intervals with durations greater than a few seconds requires higher level cognitive processes such as working memory (Ivry, 1996). Given that working memory is not properly developed in ADHD subjects due to impaired behavioural inhibition, they show deficits in their sense of time.

Proposing a dual pathway model for explaining the primary deficits in ADHD, Sonuga-Barke (Sonuga-Barke, 2002) emphasises impaired inhibitory control and aversion to delay. In an interval estimation study, Sonuga-Barke et al. (Sonuga-Barke et al., 1998) found ADHD children to significantly underestimate these time intervals, and they explain these results with the relatively fast internal clock children with ADHD have during waiting periods, leading to an aversion to delay. Considered from the perspective of a cognitive energetic approach (Sergeant, 2000; van der Meere, 2005), deficient time processing is supposed to be a consequence of impaired state regulation, seen as a mismatch between the individuals' arousal and the stimulation provided by the task (van der Meere, Shalev, Borger, & Wiersema, 2009). That is why timing related aspects such as the rate of stimulus presen-

tation and length of interstimulus intervals may be crucial for performance in ADHD. Also, the speed of internal pace making is influenced by the level of arousal (Mangels & Ivry, 2001). Finally, increased response time variability, which can be interpreted as an irregularity of timing, has been found to be the most robust neuropsychological marker of ADHD (Castellanos et al., 2005).

The striato-frontal dopaminergic system plays an important role in the neural bases of timing mechanisms (Harrington & Haaland, 1999), with the basal ganglia assumed to subtend the functioning of the "internal timer" (Gibbon, Malapani, Dale, & Gallistel, 1997; Rao, Mayer, & Harrington, 2001). According to the time processing literature, cortical and subcortical systems are involved in different cognitive components of time perception, ranging from the (subcortical) basal ganglia as a time keeper to the right inferior parietal cortex and the right dorsolateral prefrontal cortex associated with attention and working memory functions that are also mandatory for time processing, and include the thalamus as a neuroanatomical bridge for basalganglia – cortical interactions (Artieda, Pastor, Lacruz, & Obeso, 1992; Brown, 1985; Brunia & Damen, 1988; Gibbon, Church, & Meck, 1984; Harrington et al., 1998; Mohl & Pfurtscheller, 1991; Zakay, 1996). Furthermore, the cerebellum is also important for mediating time perception, and the lateral cerebellar hemisphere is involved in timekeeping mechanisms (Mangels et al., 1998).

Taken together, representations of time depend on the interplay of subcortical internal time keepers and cortical functions like attention and working memory. This leads to a complex interplay of these brain regions and different involvements of each area depending on the demands of the time processing task that can involve encoding, memory and/or decision processes.

1.4 Neurophysiology

The Contingent Negative Variation (CNV) is an electrophysiological slow brain potential wave characterized by a fronto-centrally negative polarity, and is said to be associated with temporal processing as being the on-line index of timing, that is, emerging between the beginning and the end of a to-be-estimated interval (Macar & Vidal, 2003; Macar, 2004). In terms of the timekeeper model mentioned above, the CNV amplitude is the psychophysiological correlate of a timekeeper or pulse accumulator reflected by neuronal acti-

vation generated in brain structures which underlie temporal performance (Macar, 2004). It is also and better known as to reflect anticipation processes as it slowly develops after a warning stimulus and peaks at the expected target time. Furthermore, it is related to attentional preparation (Banaschewski et al., 2004; Brandeis et al., 1998) and was found to be reduced in ADHD children during behaviourally silent waiting and preparation periods measured between cues and potential target stimuli in the cued Continuous Performance Task (CPT) (Banaschewski et al., 2003; Banaschewski et al., 2008; van Leeuwen et al., 1998).

As the CNV is mainly associated with activation in frontal cortex structures such as ACC and the supplementary motor area (SMA) (Lutcke, Gevensleben, Albrecht, & Frahm, 2008), but also influenced by subcortical structures that are involved in temporal processing (Macar, 2004) and as it emerges during a time interval of one or more seconds, it most likely reflects the cognitive system of timing, including conscious processes like inhibition or working memory.

1.5 The Search for Endophenotypes

The attempt to find stable aspects of deficits related to ADHD may be facilitated by the search for endophenotypes. This is especially true because ADHD is a heterogeneous disease with a very complex pattern of contributing factors including genes, environment and behaviour, leading to a multifactorial pattern of inheritance. Endophenotypes are biologically based phenotypes that can bridge the gap between genes underlying ADHD and the many observable facets of the disease (Doyle, Willcutt et al., 2005). As they are more closely linked to the neurobiological substrate of a disorder, they may offer the possibility to follow the complex pathways from genes to behaviour (Doyle, Faraone et al., 2005).

Various criteria for the selection of endophenotypes that are useful in finding the genetic basis of psychiatric disorders have been proposed. Some of these criteria include that 1) the endophenotype should have good psychometric properties 2) be related to the disorder, 3) be stable over time, regardless of whether or not the disorder is currently manifest, 4) be heritable and 5) should be expressed in the unaffected relatives of probands (Waldman, 2005). In addition, Castellanos et al. (2002) claim that endophenotypes should

be anchored in neuroscience to ensure the power of experimental control (Castellanos & Tannock, 2002).

In this work, we try to capture time processing with neurophysiological and neuropsychological instruments and discuss it as a possible endophenotype for ADHD.

1.6 Investigating Time Processing from a Neurophysiological and Neuropsychological Perspective

In the present studies, time processing capacities in children and adults with and without ADHD were investigated, aiming to find time processing deficits in children and adults with ADHD and thus to propose deficient aspects of time processing as stable markers or endophenotypes in ADHD.

Neurophysiological investigations (STUDY A) contained ERP measures of temporal processing (CNV) and inhibition (Nogo P300) during cued continuous performance tasks (CPT, O-X-version, plus a more demanding flanker version). Beside ERPs, performance data (mean reaction time, reaction time variability, hits and commission errors) were analyzed.

The neuropsychological approach to find stable time processing markers (STUDY B) was realized by using two time processing tasks containing time reproduction and time discrimination. In addition, classical neuropsychological tasks such as alertness, inhibition (Go/Nogo) and sustained attention (CPT) were applied.

Neuropsychological and neurophysiological methods are suitable to use in the search for endophenotypes as they measure specific brain functions affected in ADHD that might be closer related to the genes underlying ADHD than the various observable behaviours associated with ADHD. Endophenotypes of ADHD as defined by Castellanos and Tannock (Castellanos & Tannock, 2002) are essentially neuropsychological in nature. The authors distinguish three possible candidates: 1) a deficient reward system leading to shortened delay gradients, 2) a deficit in time processing expressed by response variability in speeded-reaction-time tasks, and 3) a deficit in working memory. According to this view, the inhibitory control deficit often considered as a basic neuropsychological feature of ADHD seems to be secondary to other deficits.

Neurophysiology using EEG and event related potentials is able to measure covert processes directly with millisecond accuracy and to reveal not only correlates of poor performance but also psychophysiological precursors of overt performance. Furthermore, specific differences in covert information processing can be measured even in the absence of performance differences (Banaschewski & Brandeis, 2007; Brandeis et al., 2002; Brandeis et al., 1998; van Leeuwen et al., 1998). ERP studies indicate that deficient response inhibition is preceded by altered initial orienting of attention and stimulus evaluation (Brandeis et al., 2002; Brandeis et al., 1998; Yordanova, Banaschewski, Kolev, Woerner, & Rothenberger, 2001) indicating an energetic state problem which results in poor response inhibition (Sergeant, Oosterlaan, van der Meere, 1999; van der Meere, 1996).

Thus, neurophysiological markers in combination with neuropsychological measures may be very suitable and complementing one another in investigating and differentiating stable, compensating, covert and overt cognitive processes in ADHD children and adults. Eventually, different aspects of time processing could be separated and recognized as either being associated with executive functions or with rather diffuse processes such as arousal or basal temporal perception.

1.7 Multilevel Family Assessment of ADHD

This work is embedded in a larger study investigating familial aspects of ADHD on a genetical, environmental, behavioural and neurocognitive level (The Zurich study on Multilevel Family Assesment of ADHD [MFAA; H.-Ch. Steinhausen, R. Drechsler, D. Brandeis, J. Streffer]). Families with an index child suffering from ADHD, a sibling either concordant or discordant for ADHD, and two biological parents were recruited. All family members were studied with regard to behaviour, psychopathology, and personality, selected neuropsychological tasks, brain mapping and selected candidate genes. The aim of the study is to identify endophenotypes of behavioural, neuropsychological and neurophysiological measures across two generations and to better understand the genetic and epigenetic factors contributing to familial ADHD phenotypes. Interaction with an International Multisite Genetics study of ADHD (IMAGE; Brookes et al., 2006) would allow testing the association of disease phenotypes with candidate genes.

Only an extract of this ambitious study is subject of investigation here, exploring aspects of temporal processing in children and adults with ADHD and additionally recruited age-, sex- and IQ-matched control subjects with neuropsychological and neurophysiological methods. The adult ADHD group was selected among the parents of the index children. They were allocated to the ADHD group if they reached cut-off values in two self rating scales. These subjects can be defined only subclinical as they are referred from the children with ADHD. Therefore, they cannot be considered as representative of the population of children with ADHD at adult age. Furthermore, our allocation to the ADHD adults group is based only on self-ratings. One advantage for the search for stable ADHD-markers is that the ADHD as well as the control adults are biological parents of the children, both ADHD and controls, and that they therefore share the same social background. Furthermore, stability or change of neurophysiological and neuropsychological markers can be investigated across two generations.

According to the fifth criterion for endophenotypes, which claims that it should be expressed in the unaffected relatives of probands, (Waldman, 2005), including also the nonaffected parents and nonaffected siblings of the index children in further analyses would allow investigating additional, familial aspects of possible endophenotypes. These additional groups and analyses are beyond the scope of the present dissertation but will be subject of future work by the MFAA team.

2 Study A: Differences in Neurophysiological Markers of Inhibitory and Temporal Processing Deficits in Children and Adults with ADHD

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2.1 Abstract

We compared ADHD-related temporal processing and response inhibition deficits in children and adults using event-related potentials (ERPs) during cued continuous performance tasks (CPT, O-X-version, plus a more demanding flanker version). ERP markers of temporal processing (Cue CNV) and inhibition (Nogo P300) were obtained in matched groups of children (32 with ADHD, mean age 11.2 years and 31 controls, mean age 11.1 years) and adults (22 ADHD, mean age 42.7 years and 22 controls, mean age 44.0 years). ERP markers and performance reflected both age and ADHD status. Performance was poorer, and Cue CNV and Nogo P300 were weaker in ADHD children and adults compared to their matched controls. ADHD-related ERP differences in children were more prominent at posterior scalp sites but more pronounced at anterior scalp sites in adults, paralleling the prominent topographic changes of both ERP markers with development. The fact that differences in the same test and the same processing period appear in both children and adults, but that they present in different aspects of performance and different scalp topographies,

leads to the conclusion that some ADHD-related deficits persist into adulthood despite alterations of their qualitative aspects.

Key words: Attention-Deficit / Hyperactivity Disorder, temporal processing, response inhibition, ERP, Cue CNV, Nogo P300; topography, LORETA.

2.2 Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common mental disorders of children and adolescents, and a sizable number of ADHD patients continue to be impaired in later life. The cardinal symptoms of the disorder are inattention and hyperactivity/impulsivity (Barkley, 1997). Considerable continuity of ADHD symptoms into adulthood has been demonstrated, but developmental changes of the cardinal symptoms and of task performance at the behavioural level complicate direct comparisons. Neurophysiological markers of ADHD, which are well established in children (Brandeis et al., 2002; van Leeuwen et al., 1998) and increasingly established in adults (Fallgatter et al., 2005; Wiersema, van der Meere, Antrop, & Roeyers, 2006), may be more suitable for such direct comparisons.

2.2.1 Impaired Temporal Information Processing

Impaired temporal information processing may play an important role in the deficits observed in ADHD, given that attention, inhibition and working memory are crucial for temporal processing and involve similar frontal cortex networks (Lutcke, Gevensleben, Albrecht, & Frahm, 2008; Smith, Taylor, Lidzba, & Rubia, 2003). Time processing also improves during development, thus paralleling executive functions and frontal cortex maturation (Halperin & Schulz, 2006). Similarly, frontal brain regions deviate in ADHD on structural and functional magnetic resonance imaging measures (MRI and fMRI) studies (Castellanos et al., 2002; Rubia, Smith, Brammer, Toone, & Taylor, 2005).

A major advantage of event-related EEG potential (ERP) investigations is their capability of noninvasively tracking sequences of covert cognitive processes with milliseconds precision (Banaschewski & Brandeis, 2007; Brandeis et al., 1998, 2002). Here, ERPs from a cued continuous performance test (CPT) (Rosvold, 1956) are used to disentangle brain

processes during time estimation and inhibition, compare corresponding deficits in children and adults with ADHD, and relate them to normal brain development.

The contingent negative variation (CNV) is a component with a centrally negative scalp topography slowly developing after a warning stimulus and peak at the expected target time. It is commonly considered to reflect cognitive, attentional preparation (Banaschewski et al., 2004; Brandeis et al., 1998). While the CNV has been widely studied and subdivided, the focus in the present paper is on the core CNV (i.e. the final 0.5 -1 s before target onset), and on the fact that this CNV also provides an on-line index of time processing (Macar, Anton, Bonnet, & Vidal, 2004) *per se*, without motor or inhibitory confounds. Deficits of ADHD children during behaviourally silent waiting and preparation periods are implicated by reduced amplitudes of the CNV measured between cues and potential targets stimuli in the cued CPT (Banaschewski et al., 2003; Banaschewski et al., 2008; van Leeuwen et al., 1998). In their ERP and fMRI study, Lutcke et al. (Lutcke et al., 2008) linked the CNV to frontostriatal activations including dorsal anterior cingulate (ACC) and frontal cortex regions overlapping with frontal networks activated by conflict. Furthermore, they demonstrate that an ensemble of thalamo-cortical structures is involved in CNV generation, with activation in lateral motor and premotor areas followed by activation of medial brain areas such as the anterior cingulate cortex (ACC) and the subcortical substantia nigra (SN), consistent with intracranial studies. Others also found activation in subcortical regions during the CNV, including the thalamus and the basal ganglia (Fan et al., 2007, Macar et al., 2004).

2.2.2 Impaired Inhibitory Processing

The Nogo P300 is triggered by Nogo stimuli such as the cued nontargets in the CPT that require inhibition of a prepared response, and reflects response-inhibition (Jonkman, Lansbergen, & Stauder, 2003; Smith, Taylor, Brammer, Halari, & Rubia, 2008; Strik, Fallgatter, Brandeis, & Pascual-Marqui, 1998). It is maximal at fronto-central sites and localizes to the ACC and other frontal areas (Strik et al., 1998). The Nogo P300 is smaller and less anterior in ADHD children (Banaschewski et al., 2004; Brandeis et al., 2002; Fallgatter et al., 2004) and adults (Fallgatter et al., 2005) compared to normal subjects.

The present study compares developmental and ADHD effects on temporal and inhibitory processing, using the Nogo P300 and the CNV in ADHD and control children and adults as neurophysiological markers. Our hypothesis was that ADHD-related deficits in these components - and thus deficits in inhibition and time processing - exist in both children and adults, but that these deficits undergo a structural and qualitative change because of developmental changes of the brain, especially of the frontal brain.

To investigate whether these ERP measures represent stable markers of ADHD during development, we used the continuous performance task (CPT-O-X, (Rosvold, 1956). Both the standard and the more difficult flanker version (Doehnert, Brandeis, Straub, Steinhausen, & Drechsler, 2008) allow for the distinct identification of response execution and inhibitory processing, and motor preparation and attentional orienting processes.

2.3 Methods

2.3.1 Participants

ADHD Families

A total of 158 children and 140 parents from families with at least one child suffering from ADHD gave informed consent and participated in the study. The 71 participating ADHD families consisted of both biological parents and of two children aged 8 to 16 years, with at least one sibling meeting criteria for DSM-IV combined type; several families were initially recruited in the International Multi-centre ADHD Gene (IMAGE) project (Brookes et al., 2006).

All children were free of psychotropic medication at the time of testing, and children with ADHD who were taking stimulant medication had stopped their medication at least 48 hours before the examination.

Control Subjects

The 33 control children (mean age 11.1, SD 2.1) and 32 control adults (mean age 44.7, SD 5.4) who volunteered for the study were recruited from regional elementary school, by friends or in local sport clubs.

Control and ADHD groups were matched on sex, age and IQ, resulting in 32 ADHD children (12 female), 31 control children (11 female), 22 ADHD adults (11 female) and 22 control adults (11 female) included in the analysis.

2.3.2 ADHD Assessments

Children

Rating scales used to quantify ADHD symptoms included the german versions of the Conners' Parent Rating Scale (CPRS (Conners, Sitarenios, Parker, & Epstein, 1998a)), the Conners' Teacher rating Scale (CTRS (Conners, Sitarenios, Parker, & Epstein, 1998b)) and the Strengths and Difficulties Questionnaire, parent and teacher version (SDQ, (Goodman, 1997)). T-scores ≥60 on the Conners' N-scale (DSM-IV total symptom score) were considered indicative for an ADHD diagnosis. Parents and teachers were asked to rate the behaviour of the child when off medication. The Parental Account of Children's Symptoms (PACS, (Taylor, Schachar, Thorley, & Wieselberg, 1986), a semi-structured, standardized, investigator-based interview, was administered to all probands and siblings reaching clinical scores. Children with their families were included if they met DSM-IV combined type. For detailed diagnostic procedure and algorithm see Brookes et al. (2006).

For control children, CTRS, CPRS and SDQ for both parents and teachers were completed, and non-clinical scores were required for inclusion.

Adults

Adults completed the Attention Deficit Hyperactivity Disorder-Self Report Scale (ADHD-SR (Rosler et al., 2004)) and the short form of the Wender-Utah Rating Scale (Wurs-k), a retrospective ADHD questionnaire (Retz-Junginger et al., 2003). Parents of children with ADHD who reached ≥ 15 in the ADHD-SR and ≥ 27 in the Wurs-k were

treated as ADHD adults. Control adults were included only if they scored below these cut-off values in both questionnaires.

2.3.3 Stimuli and Procedure

Measurement of IQ

Full-scale IQ was estimated by four subtests of the German version of the Wechsler Intelligence Scale for Children III (HAWIK III): Vocabulary, Block Design, Arithmetic, and Picture Arrangement (Schallberger, 2005). For adults, an IQ-estimate was calculated as the arithmetic mean of the two subtests Vocabulary and Block Design of the German Version of the Wechsler Adult Intelligence Scale (Tewes, 1991).

Neurophysiological Stimuli and Tasks / Procedure

During the test session, the probands were seated in a video-controlled, noise-shielded and slightly dimmed room on a comfortable chair. Communication between experimenter and participant during task-performance was via an intercom.

All probands started with a 5-minutes resting EEG, followed by the Standard and Flanker CPT in counter-balanced order with a different task inbetween.

The cued CPT (Rosvold, 1956) consists of 400 black letters presented on light grey (vertical visual angle 0.8°). Letters are presented for 150 ms every 1650 ms between two permanently visible vertical fixation bars. Participants had to press a button as quickly as possible with the index finger of their dominant hand whenever “O” (cue) was followed by “X” (target). This cue-target sequence (or Go-condition) occurred 40 times. Furthermore, the totally 80 cues (“O”) initiated 40 cue-nontarget sequences (“O” followed by a letter other than “X”: NoGo-condition). In the flanker version, irrelevant letters were added on both sides. Following standardized instructions, the task was practiced and comprehension ascertained. Total task duration was 11 min.

Performance measures include mean reaction time (MRT) to targets, within-subjects-variability in reaction times (RT-SD, i.e., standard deviation of latencies), and number of commission errors.

ERP Recording and Processing

The ERPs were recorded with AG/AgCl electrodes from 48 channels using SynAmps amplifier (Neuroscan, El Paso, Texas) with 500 Hz, filters set to 0.1 – 70 Hz, and calibrated technical zero baselines. Impedances were below 10 kΩ. Caps used for the montage included the standard 10-20 system positions plus the Fpz (recording reference), Oz, FT9 / 10, FC5 / 6, TP9 /10, CP5 / 6, PO9 / 10, AF1 / 2, FC1 / 2, C1 / 2, CP1 / 2, PO1 / 2, Iz and two EOG electrodes below the outer canthus of each eye. O1'/2' and Fp1'/2' were placed at 15% (5% more laterally) for more even coverage.

After downsampling to 256 Hz, the EEG was re-referenced to the average reference and filtered to 0.1 – 30 Hz (24dB/Oct). Ocular artefacts were removed using independent component analysis (ICA). Other artefacts exceeding ±100μV were rejected before averaging ERP epochs from -125ms to 1875ms. All ERP averages contained at least 20 sweeps. To avoid distorting ERP topography, no baseline subtraction was applied (van Leeuwen et al., 1998).

ERP sources were determined by using standardized low resolution electromagnetic tomography (sLORETA) (Pascual-Marqui, 2002)

Statistical Analyses

The results were analysed using SPSS version 14. Cue-CNV (mean amplitudes 1000-1600ms, i.e focusing on the core CNV) - and Nogo-P300-amplitude (414ms-574ms; based on previous work, (Doehnert, Brandeis, Imhof, Drechsler & Steinhausen, 2009)) were analyzed using a multivariate general linear model (MANOVA), with ADHD-diagnosis (ADHD vs. controls) and age (children vs. adults) as between-subjects factors, and task (Standard CPT vs. Flanker CPT) and channel (Fz, Cz and Pz both for CNV and Nogo-P300) as within-subjects factors. Topographic change in developmental lag and ADHD effects on CNV and Nogo-P300 were tested using a bootstrapping topographic analysis of variance (TANOVA) based on normalized maps and all channels (Strik et al., 1998).

For the behavioural analysis, the same groups and task factors were used, and the performance parameters hits, commission errors, mean hit reaction time (MRT) and intra-individual variability of MRT (RT-SD) were entered as multivariate within-subjects measures and subsequently tested separately.

2.4 Results

The sample characteristics of the children and adults with and without ADHD matched for age, sex and IQ are summarized in Table 1.

	Controls (C) N=31 (children); N=22 (adults)		ADHD (A) N=32 (children); N=22 (adults)		T-TEST		
	Mean	SD	Mean	SD	t	df	p
Children:							
Age [years]	11.1	2.1	11.2	2.2	-0.2	61	0.833
IQ	120.4	16.7	120.8	13.9	-0.1	61	0.917
Conners Teacher							
Attention (DSM-IV)	50.4	6.6	65.1	10.6	-6.4	59	<0.001
H / I (DSM-IV)	49.3	9.0	68.7	12.7	-6.8	59	<0.001
Total (DSM-IV)	49.7	6.5	68.8	11.2	-8.1	59	<0.001
Conners Parents							
Attention (DSM-IV)	47.2	5.1	72.7	12.3	-10.7	61	<0.001
H / I (DSM-IV)	46.3	3.8	77.6	11.9	-13.9	61	<0.001
Total (DSM-IV)	46.7	4.3	76.8	10.3	-15.0	61	<0.001
SDQ Teacher Hyperactivity	2.1	1.9	6.6	2.5	-7.9	59	<0.001
SDQ Parents Hyperactivity	1.6	1.4	7.6	2.2	-12.9	61	<0.001
Adults:							
Age [years]	44.0	4.6	42.7	4.4	1.0	42	0.332
IQ	112.6	12.7	111.7	11.9	0.2	42	0.807
ADHD-SB Sumscore	5.9	4.3	23.2	7.0	-10.0	42	<0.001
WURS-K	7.4	6.4	37.0	7.3	-14.3	42	<0.001

Table 1: ADHD and Control Subjects; Sample Characteristics

	Controls (C)		ADHD (A)		T[e]	ANOVA F(1,103)		
	Children[a]	Adults[b]	Children[c]	Adults[b]	*all children adults*			
	M(SD)[d]	M(SD)	M(SD)	M(SD)		Group (η_p^2)	Age (η_p^2)	Task (η_p^2)
MRTs for correct responses [ms]								
CPT	452.1 (81.4)	349.7 (36.6)	459.5 (92.2)	399.1 (89.9)	-1.46 -0.34 -2.39*	2.03 (0.02)	34.67*** (0.25)	34.35*** (0.00)
CPT Flanker	496.2 (78.9)	390.8 (43.8)	488.8 (98.0)	422.3 (60.2)	-0.55 0.33 -1.99+			
Standard deviation of RTs for correct responses [ms]								
CPT	153.1 (51.3)	61.3 (23.8)	167.5 (62.4)	100.3 (49.6)	-2.03* -1.00 -3.33**	10.12** (0.09)	100.29*** (0.49)	0.35 (0.56)
CPT Flanker	147.7 (45.9)	67.1 (25.5)	155.0 (45.1)	100.0 (41.5)	-1.78+ -0.63 -3.17**			
Hits								
CPT	38.3 (3.0)	39.5 (0.7)	36.4 (3.6)	38.5 (1.8)	2.85** 2.28* 2.39*	5.22* (0.05)	11.52*** (0.10)	0.22 (0.64)
CPT Flanker	37.5 (3.5)	39.1 (1.4)	37.0 (3.2)	38.4 (1.4)	1.20 0.69 1.71+			
Comission errors								
CPT	2.0 (2.6)	0.6 (1.0)	2.4 (2.9)	1.0 (1.6)	-0.96 -0.63 -1.04	2.21 (0.02)	18.15*** (0.15)	30.17*** (0.00)
CPT Flanker	3.2 (2.0)	1.6 (1.8)	5.2 (4.8)	1.6 (1.9)	-1.79+ -2.07* 0.00			

[a] N=31; [b] N=22; [c] N=32; [d] M = mean, SD = standard deviation [e] post-hoc t-tests: ADHD vs. Controls; p<0.1=+, p<0.05=*, p<0.01=**, p<0.001=***

Table 2: ADHD and Control Subjects; Performance Data

2.4.1 CPT Performance Data

The CPT performance data are summarized in Table 2. The MANOVA revealed main effects of ADHD ($F_{(4, 100)}$ =3.4, part. η^2 =.119, p =.012), Task ($F_{(4, 100)}$ =38.3, part. η^2 =.605, p =.000), Age ($F_{(4, 100)}$ =32.2, part. η^2 =.563, p =.000), and a Task x Age interaction ($F_{(4, 100)}$ =3.1, part. η^2 =.110, p =.019).

When analysing the performance measures in separate ANOVAs, ADHD subjects scored fewer hits than controls, and children had fewer hits, committed more errors and had slower and more variable MRT than adults.

Adults with ADHD missed more targets and responded slower and more variable than controls. MANOVA revealed a main effect of ADHD ($F_{(4, 39)}$ =3.8, part. η^2 =.281, p =.010) and Task ($F_{(4, 39)}$ =9.1, part. η^2 =.482, p =.000).

For children, *t*-tests showed that ADHD children made fewer hits in the CPT and committed more errors in the Flanker CPT than control children. There was no main effect of ADHD across tasks ($F_{(4, 58)}$ =1.1, part. η^2 =.073, p =.343), but a main effect of Task ($F_{(4, 58)}$ =38.3, part. η^2 =.725, p =.000).

In general, the flanker task induced more commission errors and longer MRT. This held for control children (MRT: $t_{(30)}$ = 4.4, p=.000; commission errors: $t_{(30)}$ = 3.0, p=.005), for ADHD children (MRT: $t_{(31)}$ = 2.1, p=.043; commission errors: $t_{(31)}$ = 4.4, p=.000) and for control adults (MRT: $t_{(21)}$ = 6.5, p=.000; commission errors: $t_{(21)}$ = 2.7, p=.013) - but not for ADHD adults (MRT: $t_{(21)}$ = 2.0, p=.064; commission errors: $t_{(21)}$ = 1.4, p=.180).

2.4.2 ERP-Data: Cue-CNV and Nogo P300

ERP maps of all four groups and both task variants, along with the t-maps for the ADHD and the developmental effects are illustrated in Figure 1, followed by the corresponding sLORETA solutions (Fig. 2) and waveshapes (Fig. 3).

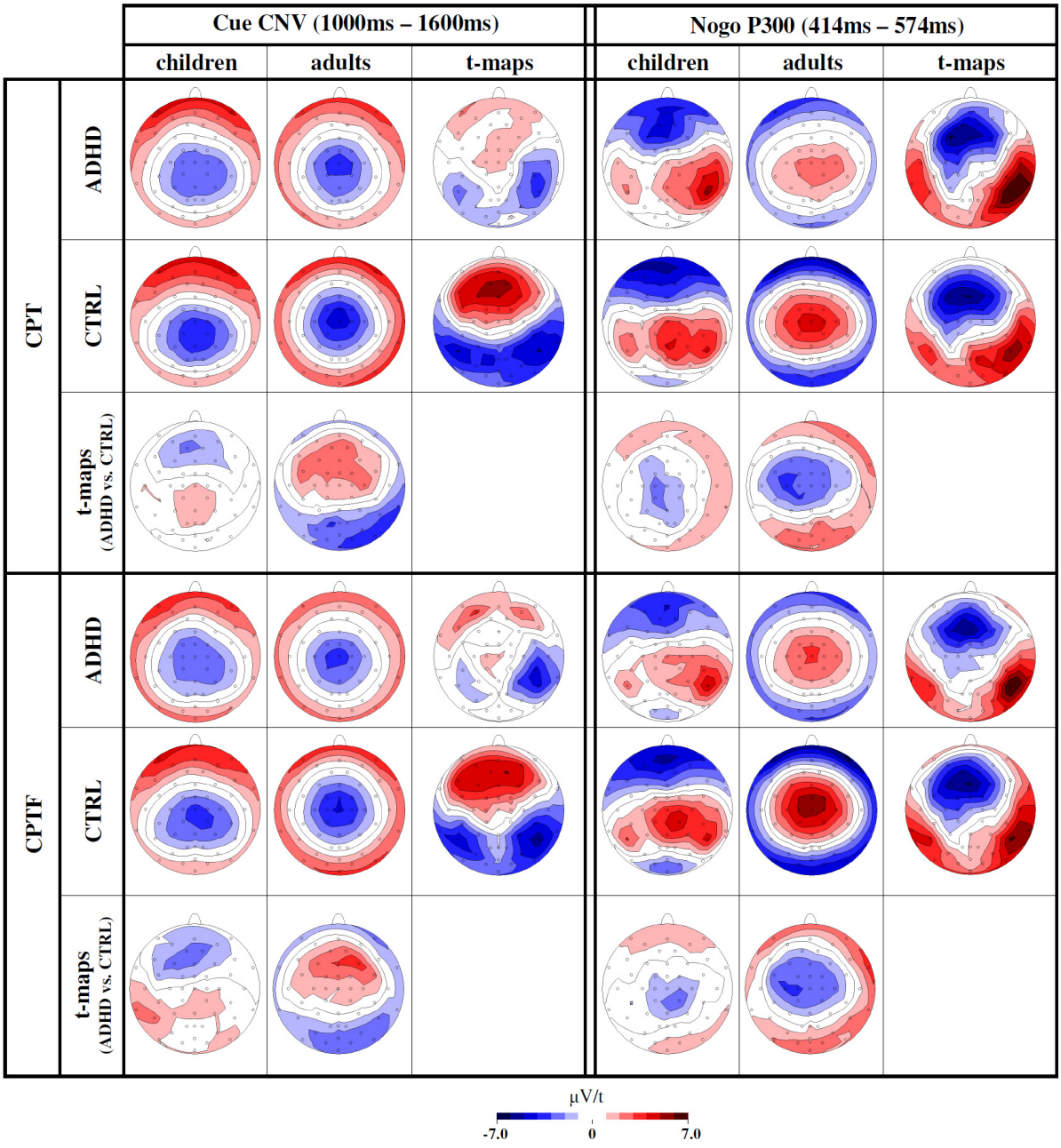

Figure 1: ERP maps by age group, ADHD status and task version, plus t-maps for age-comparison (children vs. adults) and group-comparison (ADHD vs. controls). Left: Cue-CNV during time window of 1000ms-1600ms. Right: Nogo-P300 during time window of 414ms-574ms.

The maps and t-maps (sensitive to both topographic and pure amplitude effects) are shown in Fig. 1. For the CNV, they illustrate developmental effects, particularly for controls, and different topographies of the ADHD effects in children and adults. For the Nogo P300, the maps reveal the typical fronto-central topography mainly in adults, plus prominent developmental changes regardless of ADHD status, and similar ADHD effects in children and adults.

The sLORETA tomographies (Fig. 2 top) indicate similar CNV source localisation for ADHD and control groups, but in more anterior cingulum regions for adults than children. For the NoGo P300, dominant ACC solutions are only found in adults, while children show more posterior, distributed activity. The waveshapes (Fig. 3) confirm that the developmental and ADHD-related effects for both ERP markers are not due to latency differences and are well captured by the midline electrodes and time windows selected.

Cue-CNV

The Cue CNV MANOVA indicated an interaction between ADHD, Age and Channel (Topography) ($F_{(2, 102)}$=6.5, part. η^2=.113, p =.002).

Children had less CNV negativity than adults (Age: $F_{(1, 103)}$ =6.1, part. η^2 =.056, p =.015) and CNV negativity was most pronounced at Cz, whereas positivity was most pronounced at Fz (Channel: $F_{(2, 102)}$=82.8, part. η^2=.619, p =.000). The Channel x Age interaction ($F_{(2, 102)}$=5.8, part. η^2=.102, p =.004) indicated a smaller and less anterior CNV in children than adults (less negativity at Cz and Fz). The Task x Channel interaction ($F_{(2, 102)}$ =7.2, part. η^2 =.124, p =.001) suggested that CNV negativity extended more anteriorly while frontal positivity was more pronounced in the Flanker compared to the Standard CPT, and the Task x Channel x Age interaction ($F_{(2, 102)}$=3.6, part. η^2=.066, p =.030) indicated that this pattern was only visible for children.

When tested separately, children showed ADHD x Channel ($F_{(2, 60)}$=4.4, part. η^2=.129, p =.016) and Task x Channel interactions ($F_{(2, 60)}$=8.2, part. η^2=.215, p =.001) plus a main effect of Channel ($F_{(2, 60)}$=44.8, part. η^2=.599, p =.000). ADHD children tended to have smaller (less negative) CNV than controls at Pz in the standard CPT (see t-maps in Fig. 1; $t_{(61)}$ = -1.9, p=.066) and more positivity at Fz in the Flanker CPT ($t_{(61)}$ = 2.2, p=.035). Both ADHD and control children showed an anterior shift of CNV-negativity in the flanker task compared to the standard task, with more negativity at Fz (t(62) = -3.6, p=.001) and more positivity at Pz (t(62) = 2.8, p=.008) in the Flanker CPT.

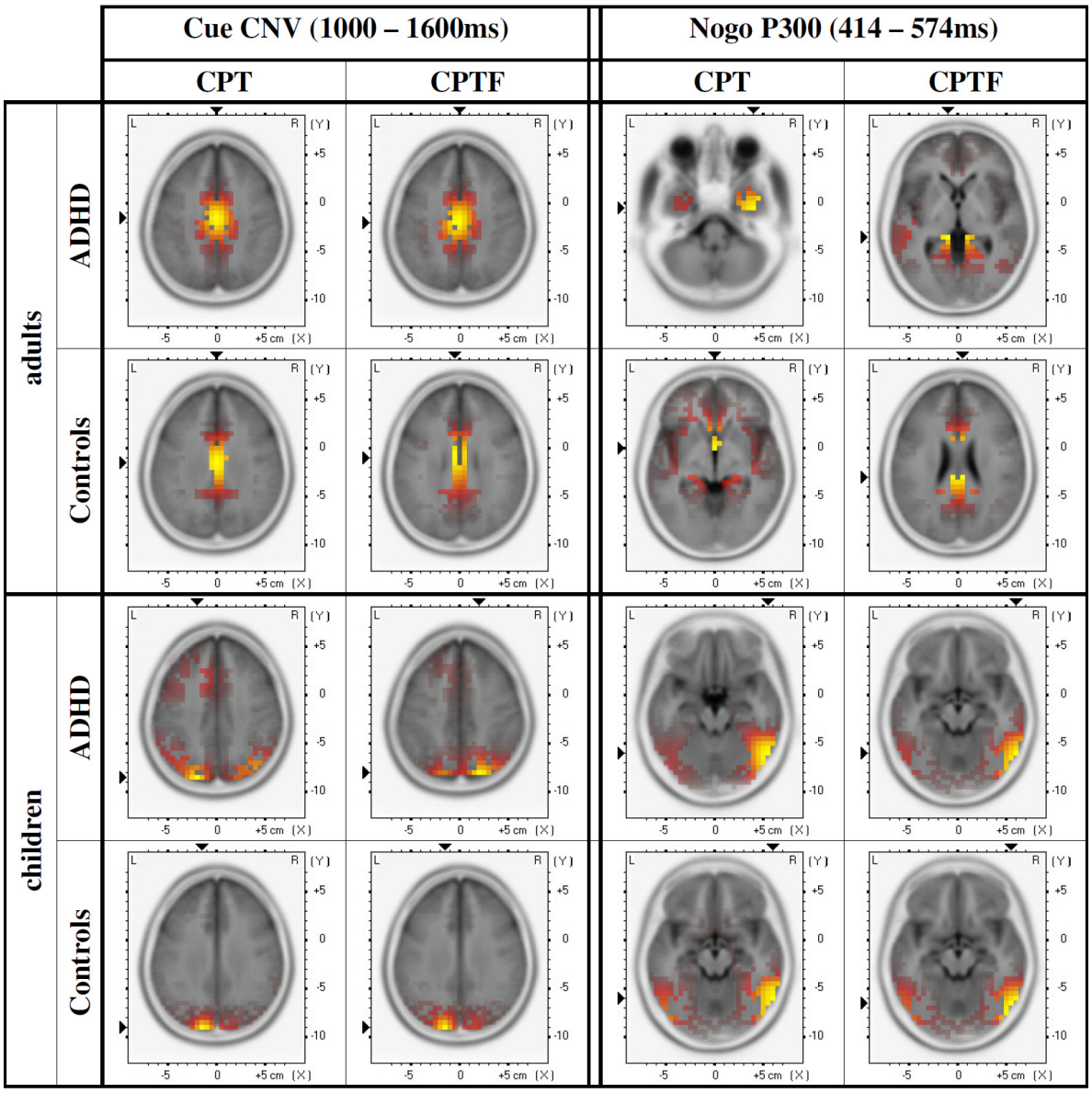

Figure 2: sLORETA: tomographic solutions (top view) for Cue-CNV (left) and the Nogo-P300 (right). Time windows etc. are as in Figure 1.

Adults showed an ADHD x Channel interaction ($F_{(2, 41)}$ =3.7, part. η^2 =.155, p =.032), indicating a CNV attenuation with ADHD at Fz ($t_{(42)}$ = -3.1, p=.003 for Flanker CPT and $t_{(42)}$ = -2.5, p=.015 for Standard CPT). The adult CNV-negativity peaked at Cz (Channel: $F_{(2, 41)}$ =56.9, part. η^2 =.735, p =.000).

The CNV-TANOVA indicated topographic developmental effects for both ADHD (p =.022) and control groups (p< .001), and topographic ADHD effects for adults (p=.011) but not children.

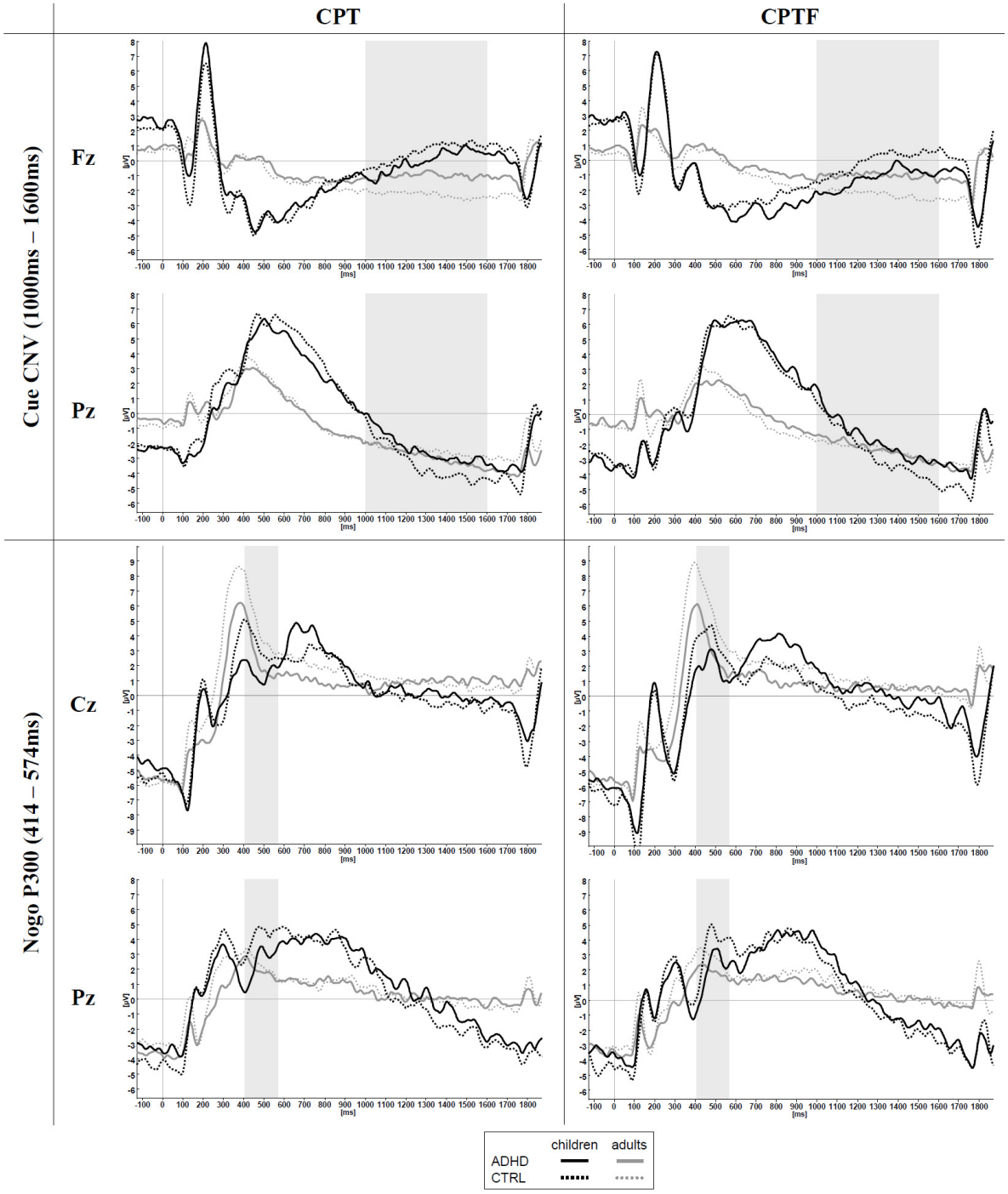

Figure 3: Above: wave shapes of the Cue-CNV at electrodes Pz and Fz.
Below: wave shapes of the Nogo-P300 at electrodes Pz and Cz.
Time windows etc. are as in Figure 1

Nogo P300

The Nogo P300 maps of all four groups, along with the t-maps for the ADHD and the developmental effects are illustrated in Figure 1.

ADHD subjects showed a weaker Nogo P300 than controls (ADHD: $F_{(1, 103)}$=12.6, part. η^2=.109, p =.001).

Children had a weaker Nogo P300 than adults (Age: $F_{(1, 103)}$=19.8, part. η^2=.161, p =.000) with a more posterior positivity (Channel x Age interaction: $F_{(2, 102)}$=24.4, part. η^2=.323, p =.000). This was visible at Fz, where adults showed positivity but children negativity ($t_{(105)}$ = -8.2, p=.000 for Flanker CPT and $t_{(105)}$ = -7.8, p=.000 for Standard CPT), and at Pz, where positivity in the Standard CPT was stronger for children than for adults ($t_{(105)}$ = 2.3, p=.024).

During the flanker task, Nogo P300 positivity was more pronounced than during the Standard CPT (task: $F_{(1, 103)}$ = 12.4, part. η^2=.107, p =.001). Separate tests for the two age groups confirmed this only for adults ($F_{(1, 42)}$=26.7, part. η^2=.389, p =.000).

Peak positivity was at Cz and was lower (for adults) or even negative (for children) at Fz (main effect of Channel: $F_{(2, 102)}$=69.8, part. η^2=.578, p =.000). Positivity was higher in the flanker task especially at Cz and Fz (channel*task: $F_{(2, 102)}$=5.4, part. η^2=.095, p =.006). Again, this interaction effect was more pronounced for adults ($F_{(2, 41)}$=4.9, part. η^2=.194, p =.012) than for children ($F_{(2, 60)}$=3.2, part. η^2=.095, p =.050).

The Nogo P300 was reduced in ADHD compared to control adults ($F_{(1, 42)}$=8.3, part. η^2=.165, p =.006) and interacted with Channel ($F_{(2, 41)}$=3.4, part. η^2=.143, p =.042). Control adults had a stronger Nogo P300 at Fz ($t_{(42)}$ = 2.5, p=.018 for Flanker CPT and $t_{(42)}$ = 2.2, p=.035 for Standard CPT) and Cz ($t_{(42)}$ = 2.7, p=.009 for Flanker CPT and $t_{(42)}$ = 2.6, p=.013 for Standard CPT) than ADHD adults.

For children, the Nogo P300 reduction with ADHD ($F_{(1, 61)}$=5.2, part. η^2=.078, p =.026) was observed at Pz ($t_{(61)}$ = 1.8, p=.075 for Flanker CPT and $t_{(61)}$ = 2.0, p=.049 for Standard CPT).

The Nogo-P300-TANOVA indicated topographic developmental effects for both ADHD and control groups (both p< .001), and topographic ADHD effects for children only (p=.042).

2.5 Discussion

We assessed performance and neural ERP markers of time processing and inhibition in children and adults with ADHD compared to matched controls in the same task, and found similar but not identical ADHD-related deficits across age. Children as well as adults with ADHD showed impairments in their overt task performance and their covert cognitive-electrophysiological processing. This was true even though adult ADHD "diagnoses" were only based on self-ratings (plus familial ADHD). Differences in the same test and processing steps thus appeared in both children and adults but affected different aspects of performance and differed in scalp topography, indicating that ADHD-related deficits continue into adulthood despite being modulated by developmental changes.

2.5.1 Performance

Individuals with ADHD performed more poorly than controls. Separate analyses comparing Standard CPT and Flanker CPT performance indicated main effects of ADHD only for adults, with greater RT variability, slower MRTs, and fewer hits in ADHD than in control adults. Especially the RT-SD-differences are in line with previous findings of behavioral variability in ADHD (Steger et al., 2001).

As expected, adults performed better than children, consistent with a large body of evidence on developmental improvements of attention and inhibition (Casey, Giedd, & Thomas, 2000; Jonkman et al., 2003). The Flanker CPT proved more demanding than the Standard CPT, in line with our previous comparisons of these two CPT versions (Doehnert et al., 2008), and with much previous work documenting strong interference from flankers surrounding central targets in a variety of attentional tasks (Albrecht et al., 2008; Eriksen; Fan, Flombaum, McCandliss, Thomas, & Posner, 2003; van Mourik et al., 2009).

Like in other studies, aspects of CPT performance were impaired in ADHD even after controlling for IQ. However, our neurophysiological markers of ADHD on correct trials do not depend on such performance differences. They reflect covert attentional processes which may be more robust than performance measures because they are less susceptible to compensatory processes and variability from other, confounding processes.

2.5.2 Cue-CNV

The developmental change toward a more anterior CNV topography was well reflected by the tomography and interacted with ADHD, indicating that CNV-differences between ADHD-subjects and controls differed for children and adults. While ADHD children's CNV was reduced at posterior sites, the CNV-attenuation in ADHD adults mainly affected more frontal sites. These results are in line with other studies reporting a weaker posterior CNV in children with ADHD compared to controls (Banaschewski et al., 2003; Dumais-Huber, 1992; Hennighausen, Schulte-Korne, Warnke, & Remschmidt, 2000), and developmental CNV changes (Bender, Weisbrod, Bornfleth, Resch, & Oelkers-Ax, 2005; Jonkman et al., 2003).

The CNV time window selected here is comparable with the late CNV defined by Lutcke et al (2008). ADHD effects on this CNV of children and adults have never before been compared directly. Our results show that topographies differ and suggest a developmental change of ADHD-related impairments. While brain regions associated with CNV, such as dorsolateral prefrontal cortex and ACC (Gomez, Marco, & Grau, 2003; Lutcke et al., 2008) develop along with improving attentional functions after childhood (Jonkman et al., 2003), the CNV differences between healthy adults and adults with ADHD persist. Since the CNV is a composite of several generators, it is possible that this continued CNV amplitude reduction in ADHD adults reflects the influence of subcortical rather than cortical generators and is related to aspects of pure time processing associated with the CNV rather than to executive aspects.

The children's more anterior CNV in the Flanker CPT compared to the easier Standard CPT resembles a shift toward a more adult-like pattern. This anterior CNV shift with difficulty could not be seen in adults, and could indicate that children when challenged can invoke a more mature processing during their preparatory processing. While this topographic effect can be seen in the maps as a subtle shift of the negative center of gravity, it is not evident in the tomographic solutions, possibly due to a lack of sensitivity to such subtle changes.

The more anterior CNV in adults than in children was evident in maps and tomographies, and is in line with previous developmental CNV findings that left frontocentral late CNV negativity only appeared after age 11 in adolescents which has been interpreted to

reflect the relatively late development of brain areas involved in response preparation (Bender et al., 2005). As the children in the present study were at an age where these brain areas might just start to develop, the more challenging flanker CPT may have prompted them to engage a more "adult" pathway, resulting in a more adult-like anterior CNV topography.

2.5.3 Nogo P300

The ADHD effects on the Nogo P300 interacted with age as they were modulated by the anterior topographic shift of the positivity in adults. Both maps and tomographies suggest that this shift is due to the lack of dominant ACC activation in children whose posterior activity still dominated. When tested separately, ADHD effects remained significant for both adults and children but a task effect was found only for adults. It seems that, for adults, the CPT versions activate partly distinct processes, but both detect covert differences in response inhibition between controls and ADHD adults even though these are more pronounced with the Flanker CPT. The late Nogo P300 time window of Doehnert et al.(2009) was selected because it showed a central negativity in all tasks and groups. This window also showed ADHD-related Nogo P300 effects in both children and adults, while the early Nogo P300 window showed ADHD-related effects only in adults. Although this late time window was past the peak of the Nogo P300 for the adults and for the simple CPT (Fig. 3), the fronto-central Nogo P300 topography was still evident (Fig. 1), and the developmental effects were similar in both windows.

2.6 Conclusion

This work compares for the first time ERP markers of ADHD reflecting time processing or preparation and inhibition in children and adults with and without ADHD. The results indicate that despite strong developmental effects on the Nogo P300 and CNV, ADHD-effects were present both in children and adults; however, these differences were even more pronounced in adults and agreed with an altered topography reflecting a shift from posterior to anterior sites. It seems that ADHD-deficits concerning temporal preparation and inhibition persist into adulthood even though the active networks change and follow developmental changes of the normal brain.

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3 Study B: Time processing in children and adults with ADHD

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Submitted.

3.1 Abstract

A time processing deficit has been proposed as a neuropsychological candidate endophenotype for ADHD, but its developmental trajectory and its possible overlap with other deficits still need to be explored. In the present study, children (N=33) and adults (N=22) with ADHD were compared to normal controls on two time processing tasks. Time reproduction was impaired in ADHD, with quantitative rather than qualitative differences between affected children and adults. In the discrimination of brief intervals, children and adults with ADHD showed different deficit patterns. We conclude that time processing deficits in ADHD persist into adulthood, but may take on age-related different forms.

Key words: ADHD, time processing, neuropsychological endophenotype, time reproduction, time discrimination

3.2 Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common mental disorders of children and adolescents, and a sizable number of ADHD patients continue to

be affected with impaired psychosocial behaviour in later life. The strong familial and genetic component of ADHD (Rhee, Waldman, Hay, & Levy, 1999; Sherman, Iacono, & McGue, 1997), its links to an imbalance of specific neurotransmitter systems such as dopamine (Faraone, Doyle, Mick, & Biederman, 2001; Lowe et al., 2004) and noradrenaline (Biederman & Spencer, 1999; Gainetdinov et al., 1999) and the presence of neuropsychological (Barkley, 1997; Klimkeit, Mattingley, Sheppard, Lee, & Bradshaw, 2005) as well as neurophysiological (Brandeis et al., 2002; van Leeuwen et al., 1998) markers of ADHD is well established.

Numerous studies have investigated aspects of time processing in ADHD such as time estimation, duration discrimination, temporal (re-) production and motor timing (Barkley, Koplowitz, Anderson, & McMurray, 1997; McInerney & Kerns, 2003; Smith, Taylor, Brammer, Halari, & Rubia, 2008; Smith, Taylor, Rogers, Newman, & Rubia, 2002). They provide overwhelming evidence that individuals with ADHD have problems with temporal processing, though results are inconsistent for some specific aspects like verbal estimation or anticipation (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Barkley, Murphy, & Bush, 2001; Meaux & Chelonis, 2003; Radonovich & Mostofsky, 2004; Rubia, Noorloos, Smith, Gunning, & Sergeant, 2003).

Different theoretical approaches have provided explanations for time processing deficits in ADHD. According to Barkley et al. (1997), impaired time processing in ADHD subjects is a consequence of impaired response inhibition and executive function deficits. The reproduction of time intervals with durations greater than a few seconds requires higher level cognitive processes such as working memory (Barkley, Murphy et al., 2001; Ivry, 1996) which is often impaired in ADHD, and the characteristic underproduction of intervals observed in ADHD with increasing interval length has been linked to inhibitory control deficits. In his dual pathway model, Sonuga-Barke proposes motivational impairment due to delay aversion as an additional explanatory hypothesis. This model accounts for the heterogeneity of neuropsychological impairment associated with ADHD, as only a subgroup of children present clinically relevant problems in the executive function domain (Sonuga-Barke, 2002). In an interval estimation study, Sonuga-Barke et al. (1998) found ADHD children to significantly underestimate these time intervals, and propose that children with ADHD have an internal clock running too fast during waiting periods, leading to an aversion to delay. In a third theory, the cognitive energetic approach (see Sergeant,

2000; van der Meere, 2005), deficient time processing is supposed to be a consequence of impaired state regulation, which can be conceptualized as a mismatch between the individuals' arousal and the stimulation provided by the task (van der Meere, Shalev, Borger, & Wiersema, 2009). That is why timing related aspects such as the rate of stimulus presentation and the length of interstimulus intervals may be crucial for performance in ADHD. Also, the speed of internal pacemakers is influenced by the level of arousal (Mangels & Ivry, 2001). Finally, increased response time variability – which can be interpreted as an irregularity of timing - has been found to be the most robust neuropsychological marker of ADHD (Castellanos et al., 2005), but for limitations see Geurts et al., (2008)). Lapses of attention as well as impaired response preparation seem both to contribute to this phenomenon (Vaurio, Simmonds, & Mostofsky, 2009), which has been linked to spontaneous fluctuations in brain activity (see Di Martino et al., 2008; Rothenberger, 2009) or to dysfunctional premotor circuits (Suskauer, Simmonds, Caffo et al., 2008; Suskauer, Simmonds, Fotedar et al., 2008).

Impaired temporal processing has also been proposed as a distinct neuropsychological candidate endophenotype for ADHD (Castellanos et al., 2002). Rommelse et al. report that children with ADHD as well as their non-affected siblings are impaired on a time reproduction task and conclude that time reproduction should be considered a candidate endophenotype (Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant, 2007). In a recent study contrasting duration discrimination in the milliseconds and seconds range, Himpel and coworkers found that children with ADHD are impaired in discriminating both brief and longer intervals, but non-affected siblings only in discriminating brief intervals. In consequence the authors propose the discrimination of brief intervals as a marker of vulnerability or endophenotype for ADHD (Himpel et al., 2009).

There is agreement on the existence of two distinct systems of temporal processing: the more "automatic" system for timing in the milliseconds range computed by the cerebellum and basal ganglia is also considered important for motor coordination and (Harrington, Haaland, & Hermanowicz, 1998). The more "cognitive" system for timing in the seconds to minutes range computed by frontal-striatal circuits which also support working memory functions is supposed to be important for temporal estimation and reproduction and (Karmarkar & Buonomano, 2007; Lewis & Miall, 2003a, 2003b, 2006; Madison, 2001). Thus, temporal processing in the range of milliseconds should not primarily depend on

working memory and attentional allocation abilities nor on motivational aspects, in contrast to temporal processing of time intervals longer than 1 second (Mangels, Ivry, & Shimizu, 1998). So far, impairments of either system are compatible with experimental findings in ADHD and supported by neurobiological models as well as by imagery studies (for reviews see Durston, de Zeeuw, & Staal, 2009; Giedd, Blumenthal, Molloy, & Castellanos, 2001; Kelly, Margulies, & Castellanos, 2007; Kieling, Goncalves, Tannock, & Castellanos, 2008; Willis & Weiler, 2005).

Only few studies have investigated temporal processing in young adults with ADHD, largely replicating findings from childhood samples for time reproduction, at least in males (Barkley, Murphy et al., 2001; Seri, Kofman, & Shay, 2002). A recent investigation of rhythmic performance in young adults with ADHD revealed difficulties only at a medium speed (Gilden & Marusich, 2009), suggesting that internal clock mechanisms continue to be partly compromised in adulthood. To our knowledge, however, there is no study including adults with ADHD older than 30 years. Therefore the developmental course of temporal processing deficits in ADHD still needs to be explored and so far, it is unknown to which extent difficulties with time processing persist in later adulthood.

Neuropsychological studies on adult ADHD usually include clinically referred adults who may not be representative of the typical course of childhood ADHD into adulthood in the general population. While a majority of these studies report heterogeneous neuropsychological impairment similar to that of childhood ADHD (Balint et al., 2009; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Hervey, Epstein, & Curry, 2004; Schoechlin & Engel, 2005; Seidman, 2006), some studies find age-related changes (Tucha et al., 2008). Follow-up studies which are more informative regarding the natural course have shown that executive function deficits seem to persist into adulthood, but only with full ADHD status and under the premise that EF deficits were already present in childhood (Biederman et al., 2007; Halperin, Trampush, Miller, Marks, & Newcorn, 2008). Halperin et al. (2006)) claim that with maturation, frontally mediated executive functions will compensate for primary and enduring subcortical deficits in many individuals with ADHD and lead to a reduction of ADHD symptoms in adulthood. Neuropsychological deficits that are not under conscious control, however, should remain stable, irrespective of general improvement due to maturation and behavioural adaptation. Thus, one might expect differential developmental trajec-

tories for tasks such as time reproduction taxing more executive aspects of time processing, and tasks tapping more basal internal clock mechanisms.

The purpose of the current study was to examine the performance of both children and adults with ADHD in a time reproduction and a time discrimination task in order to investigate the stability of the deficits over time. We hypothesized that children as well as adults with ADHD would show deficits in temporal processing compared to matched controls, but with somewhat differential pattern of impairment according to the employed task paradigms. Both children and adults should show significant impairment in a time discrimination task where target intervals are in the range of milliseconds. Here, performance is supposed to be largely independent from inhibitory control and motor components and representative of basal timing mechanisms. On the time reproduction task, with durations up to several seconds, one would expect adults with ADHD to show minor deficits if at all when compared to matched controls, whereas children with ADHD should show a clear underproduction of durations, especially with longer intervals to be reproduced. In line with this argumentation, we expect time reproduction performance to be correlated with inhibitory control measures and time discrimination performance with neuropsychological measures of arousal or sustained attention.

3.3 Method

3.3.1 Subjects/participants

Children and Adults with ADHD

Children and adults with ADHD were participants of the Zurich Multimodal Family Assessment Study on ADHD (MFAA). For this study, families with at least one child suffering from ADHD (DSM-IV combined type) were recruited in the Department of Child and Adolescent Psychiatry in Zurich or via a Swiss organisation for parents of children with ADHD. The study also had somebenefits from interactions with the International Multicentre ADHD Gene (IMAGE) project (Brookes et al., 2006), which aims at investigating the genetic transmission of ADHD.

Children with ADHD: 33 children with ADHD (20 boys, and 13 girls, age range 8 to 15 years) were included in the study. Inclusion criteria were the diagnosis of ADHD combined subtype (DSM-IV), IQ of at least 80, absence of known neurological or other psychiatric diseases. The German versions of the Conners' Parent Rating Scale (CPRS-R:L) (Conners, Sitarenios, Parker, & Epstein, 1998a) and the Conners' Teacher Rating Scale (CTRS-R:L) (Conners, Sitarenios, Parker, & Epstein, 1998b) were used as screening instruments at the first stage. For children scoring above the clinical threshold on one of these questionnaires, the Parental Account of Children's Symptoms (PACS) interview (Taylor, Schachar, Thorley, & Wieselberg, 1986) was administered by a trained interviewer. PACS is a semi-structured, standardized, investigator-based clinical interview. DSM-IV-diagnosis was derived by an algorithm combining PACS interview and Conners' Teacher Rating Scale data, adopted from the HYPESCHEME procedure of the IMAGE study (Brookes et al., 2006). For a description of the sample see Table 1.

Adults with ADHD: The 22 adults (11 male and 11 female, age range 32 to 52 years) with ADHD participating in this study were identified among the parents of children with ADHD. Inclusion criteria were scores within the clinical range on an ADHD-self-rating questionnaire for adults on current ADHD-symptoms (ADHS-SB, (Rosler et al., 2004) as well as on a retrospective self-rating questionnaire on ADHD childhood symptoms (German short form of the Wender-Utah Rating Scale, WURS-k, (Retz-Junginger et al., 2003). All participants taking stimulants (15 children and 4 adults) had interrupted medication at least 48 hours before testing.

Control Subjects

33 control children and 22 control adults volunteered for the study. They were recruited from various sources, including regional elementary school, and local sport clubs. Control subjects who scored above the clinical cut-off on any of the questionnaires used for ADHD diagnosis in children or adults were excluded.

Controls and ADHD subjects were matched pairwise according to sex, age, and IQ (see Table 1). Before entering the study, all children and adults gave their informed consent. The study was approved by the local ethics committee.

	ADHD (A) N=33(children); N=22(adults)		Controls (C) N=33(children); N=22(adults)		t-test
	Mean	SD	Mean	SD	p
Children:					
Age [years]	11.0	2.1	11.0	2.1	0.992
Sex (male/female)	20/13		20/13		
Estimated IQ	119.6	15.4	120.7	16.3	0.783
Conners Teacher					
Attention (DSM-IV)	65.4	10.6	51.0	7.3	<0.001
H / I (DSM-IV)	68.5	12.6	49.3	8.7	<0.001
Total (DSM-IV)	68.9	11.0	50.1	6.7	<0.001
Conners Parents					
Attention (DSM-IV)	72.3	12.3	47.3	5	<0.001
H / I (DSM-IV)	77.4	11.8	46.3	3.7	<0.001
Total (DSM-IV)	76.4	10.4	46.7	4.2	<0.001
SDQ Teacher Hyperactivity	6.6	2.5	2.2	1.8	<0.001
SDQ Parents Hyperactivity	7.5	2.3	1.6	1.4	<0.001
Adults:					
Age [years]	42.2	4.4	43.5	4.5	0.304
Sex (male/female)	11/11		11/11		
Estimated IQ	111.1	11.4	111.6	12.4	0.880
ADHS-SB Sumscore	23.0	6.9	6.2	4.2	<0.001
WURS-K	35.7	7.4	7.2	5.9	<0.001

Conners Teacher = Conners' Teacher Rating Scale (CTRS-R:L), Conners Parents = Conners' Parent Rating Scale (CPRS-R:L), H/I= Hyperactivity/Inattention score, SDQ= Strengths and Difficulties Questionnaire, ADHS-SB= ADHD Self-Report Scale (Rösler et al., 2003), WURS-K = Wender-Utah-Rating Scale-short form

Table 3: ADHD and control subjects; sample characteristics

3.3.2 Instruments

Time Reproduction Task

In the time reproduction task, participants were instructed to remember the duration of a visually presented beacon from a lighthouse and to stop an immediately following beacon after exactly the same time period by pressing the left mouse button. The presented beacons varied in their durations and lasted either 1, 2, 3, 4, 6, or 8 seconds (Figure 1). Standardized verbal and visual instructions were used. Testing started following a practice block of 5 trials with feedback after each response. Thereafter, 60 experimental trials were administered. Each of the six interval lengths was randomly presented ten times. Participants did not receive feedback during the test block.

Time Discrimination Task

Performance on duration discrimination was assessed by presenting consecutively two visual stimuli which differed in their presentation by 50 to 500 ms. Half of the total of 72 stimulus-pairs differed by 100ms or less (difficult condition) while the other half differed by 200ms or more (easy condition). Presentation time of each stimulus varied from 450 to 1000 ms. Participants were asked to press the left mouse button if the first, and the right mouse button if the second stimulus had lasted longer. Standardized verbal and visual instructions were used. Testing started following a practice block where individuals received feedback whether their answers were right or wrong. During the test block no feedback was given (Figure 1).

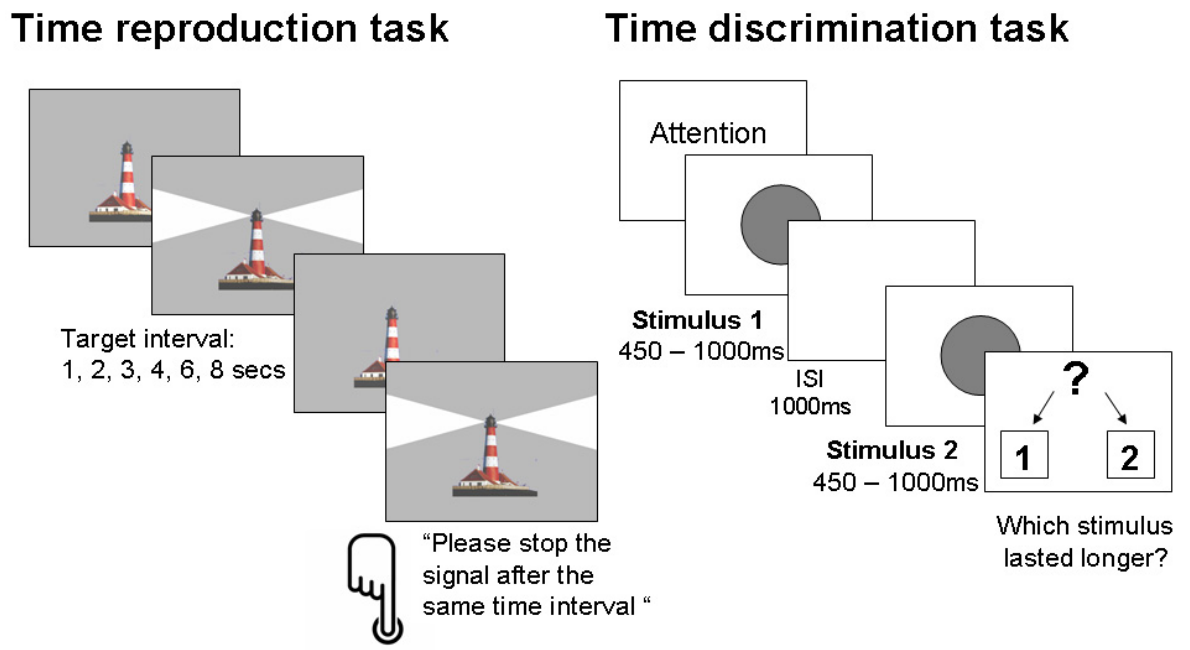

Figure 4: Time reproduction task and time discrimination task.
Time Reproduction Task: Presented beacons of the light house lasted 1, 2, 3, 4, 6 or 8 seconds. These intervals had to be reproduced by the participants by pressing the mouse button after the corresponding amount of time.
Time Discrimination Task: Participants had to decide which one of two subsequently presented stimuli lasted longer. Stimulus 1 and stimulus 2 differed in their duration be-tween 50 ms and 500 ms. Differences of duration were ≤100 ms in half of the trials, ≥ 200 in the other half.

Neuropsychological Tests

In addition, participants performed several classical neuropsychological tasks: a simple motor response task (Alertness), an inhibition task (Go/Nogo) and a cued continuous performance task (CPT O-X). The alertness and inhibition task were taken from the *Test for Attentional Performance TAP* (Zimmermann, 2002) which is a standardized computerized instrument that has been evaluated for the assessment of children and adults with ADHD (Földenyi, 2000; Tucha et al., 2008).

In the Alertness task, participants responded as quickly as possible to a visually presented stimulus (presentation of a cross in the centre of a computer screen) that remained visible until the response is collected. Half of these trials also contained an acoustic warning signal preceding the target stimulus by 600 to 1500 ms. The task was divided into four blocks of 20 stimuli; two blocks with and two blocks without acoustic warning signal.

In the Go/Nogo task, participants had to respond as quickly as possible to a Go-stimulus as represented by an "x", and have to ignore the Nogo-stimulus as represented by

a “+”, both presented in the centre of the screen for 2000 msec. From a total of 40 trials, 50% are Go- and 50% Nogo-trials. The cued Continuous Performance Task (Rosvold, 1956; Doehnert, Brandeis, Straub, Steinhausen, & Drechsler, 2008; van Leeuwen et al., 1998) was part of the neurophysiological investigation which is described in detail in Valko et al. (submitted). It consists of 400 black letters which are presented for 150 ms every 1650 ms between two permanently visible vertical fixation bars. Participants had to press a button as quickly as possible whenever “O” (cue) was followed by “X” (target). This cue-target sequence or Go-condition occurred 40 times (10%). The other 40 cues initiated cue-nontarget sequences (“O” followed by a letter other than “X”: Nogo-condition).

Questionnaires and IQ

Assessment tools used to quantify ADHD symptoms in children included the German version of the Conners’ Parent Rating Scale (CPRS-R:L, Conners et al. 1998a), the Conners’ Teacher Rating Scale (CTRS-R:L, Conners et al. 1998b), the Strengths and Difficulties Questionnaire, parent and teacher version (SDQ, Goodman, 1997), and the PACS Interview (PACS, Chen & Taylor, 2006). Adults completed the Attention Deficit Hyperactivity Disorder-Self Report Scale (ADHS-SB, Rösler et al., 2004) and the German short form of the Wender-Utah Rating Scale (WURS-k) (Retz-Junginger et al., 2003). In children, IQ was estimated by four subtests of the German version of the Wechsler Intelligence Scale for Children III: Vocabulary, Block design, Arithmetic, and Picture Arrangement (Schallberger, 2005). In adults, IQ-estimation was calculated by taking the arithmetic mean of the German WAIS subtests Vocabulary and Block Design (Tewes, 1991).

3.3.3 Procedure

The neuropsychological testing of the subjects with ADHD took place at the Department of Child and Adolescent Psychiatry in Zurich. Neuropsychological testing of controls took place either at the Department, at school, or at their home. Except for the CPT, all tests were administered on the same day.

3.3.4 Statistical Analyses

The results were analyzed using SPSS version 14. For the time reproduction task, mean reaction times of the reproductions of different target intervals (MRT) and standard deviations of mean reaction times (RT-SD) were analyzed using a multivariate general linear model (MANOVA), with group (ADHD vs. controls) and age (children vs. adults) as between-subjects factors, and mean reaction times (MRT) and variability of reaction times (RT-SD) as multivariate within-subjects measures. The interval lengths (six intervals: 1, 2, 3, 4, 6, 8 seconds) were treated as repeated measures. For the time discrimination task, the same between-subjects factors were used, duration difference (trials with a difference of less than 100ms vs. trials with a difference of 200 ms or more) was used as repeated measure, and the mean reaction time (MRT), reaction time variability (RT-SD), and number of correct responses (hits) were entered as within-subjects measures. Subsequently, post hoc t-tests for group and age effects and separate MANOVAS for the children and the adults groups with univariate and post hoc t-tests were carried out.

Neuropsychological tests were analyzed by MANOVA or ANOVA. For the Alertness task, group and age were entered as between-subjects factors and Median RT (MD) and RT-SD as within-subjects measures, and trials with or without warning tone (condition) as repeated measures. For the Go/Nogo task, MRT, RT-SD and errors were entered as dependent variables. For the CPT, an ANOVA was calculated with group (ADHD versus controls) and age (children versus adults) as between-subjects factor and hits, commission errors, mean reaction times (MRT) and variability of reaction times (RT-SD) as dependent variables. A z-transformation was applied to all four tasks.

Scores from questionnaires were compared by t-tests. In an exploratory analysis, composite scores from the time reproduction task (total MRT = sum of z-transformed mean reaction times, total SD = sum of z-transformed SDs of 1, 2, 3, 4, 6, 8 secs. interval duration) and the time discrimination task (total hits, total MRT) were correlated separately for children and adults with parameters from Alertness, Go/Nogo and the CPT in partial correlations controlling for age.

3.4 Results

3.4.1 Time Reproduction

The MANOVA revealed a significant main effect of ADHD ($F_{(2, 105)}$ =4.9, part. η^2 =.085, p =.009) and age ($F_{(2, 105)}$ =13.9, part. η^2 =.209, p =.000), but no significant interaction of ADHD by age. Univariate tests revealed that the main-effect of ADHD was caused both by increased RT-SD ($F_{(1, 106)}$ =6.4, part. η^2 =.057, p =.013) and underestimated mean reproduction of time intervals ($F_{(1, 106)}$ =5.4, part. η^2 =.049, p =.022). Post-hoc t-tests showed that ADHD subjects differed significantly stronger from the target intervals than control subjects by underreproducing the time intervals of 4, 6 and 8 secs (for 4sec: $t_{(108)}$ = 2.3, p=.022; for 6sec: $t_{(108)}$ = 2.9, p=.005; for 8sec: $t_{(108)}$ = 2.8, p=.005) and by being more variable in their mean reaction times when reproducing intervals of 2 secs ($t_{(108)}$ = 2.2, p= .029), 4 secs ($t_{(108)}$ = 2.0, p= .047) and 8 secs ($t_{(108)}$ = 2.4, p=.019). At the interval of 6 secs, only a trend towards increased RT-SD in ADHD subjects was found ($t_{(108)}$ = 1.9, p=.065); cf. Table 2.

	Children (N=33/33)			Post hoc t-test [b] N=33/33	Adults (N=22/22)			Post hoc t-test [c] N=22/22	Post hoc t-tests [a] N=55/55
	ADHD M(SD)		Con-trols M(SD)		ADHD M(SD)		Con-trols M(SD)		
Time Reproduction Task									
Mean of reaction times [ms]									
1000ms	992 (219)		962(218)	n.s.	965 (229)		1007 (223)	n.s.	n.s.
2000ms	1939 (355)		1907 (234)	n.s.	1869 (170)		1968 (247)	n.s.	n.s.
3000ms	2723 (404)		2813 (286)	n.s.	2750 (350)		2869 (217)	n.s.	n.s.
4000ms	3619 (550)		3808 (366)	n.s.	3642 (382)		3822 (310)	+	*
6000ms	5266 (599)		5650 (344)	**	5644 (366)		5619 (377)	n.s.	**
8000ms	6852 (864)		7345 (560)	**	7345 (700)		7538 (381)	n.s.	**
SD of reaction times [ms]									
1000ms	488 (307)		391 (281)	n.s.	320 (305)		247 (242)	n.s.	n.s.
2000ms	585 (354)		404 (265)	*	309 (148)		291 (102)	n.s.	*
3000ms	559 (271)		522 (295)	n.s.	409 (245)		338 (122)	n.s.	n.s.
4000ms	786 (492)		610 (330)	+	437 (228)		339 (150)	n.s.	*
6000ms	968 (609)		739 (451)	+	502 (280)		421 (133)	n.s.	*
8000ms	1248 (821)		885 (696)	+	797 (674)		556 (235)	n.s.	*
Time Discrimination Task									
Hits									
difference ≤ 100ms	20.9 (4.2)		22.2 (2.9)	n.s.	24.0 (3.5)		26.0 (3.5)	+	*
difference ≥ 200ms	27.0 (5.3)		30.2 (4.4)	**	32.0 (6.6)		33.6 (5.0)	n.s.	*
SD of reaction times [ms]									
difference ≤ 100ms	911 (422)		984 (404)	n.s.	640 (414)		399 (268)	*	n.s.
difference ≥ 200ms	871 (478)		923 (498)	n.s.	551 (345)		401 (254)	n.s.	n.s.

Table 4: Results of time processing tasks

The main effect for age was caused by decreasing RT-SD only ($F_{(1, 106)}$ =28.0, part. η^2 =.209, p =.000): Children, compared to adults, showed significantly larger RT-SDs in the reproduction of all six time intervals (for 1sec: $t_{(108)}$ = 2.4, p=.016; for 2 secs: $t_{(108)}$ = 4.4,

p=.000; for 3 secs: $t_{(108)}$ = 3.7, p=.000; for 4 secs: $t_{(108)}$ = 5.2, p=.000; for 6 secs: $t_{(108)}$ = 5.2, p=.000; for 8 secs: $t_{(108)}$ = 3.2, p=.002).

When analyzing children and adults separately, the ADHD effect remained solely in the children group (children: $F_{(2, 63)}$ =3.6, part. η^2 =.102, p =.034; adults: $F_{(2, 41)}$ =1.9, part. η^2 =.087, p =.156). Children with ADHD performed slightly poorer in their time reproductions ($F_{(1, 64)}$ =3.5, part. η^2 =.051, p =.068) by underreproducing intervals, especially at 6 secs ($t_{(64)}$ = -3.1, p= .003) and 8 secs ($t_{(64)}$ = -2.8, p= .008) and showed larger variability in their reaction times ($F_{(1, 64)}$ =4.9, part. η^2 =.071, p =.031), when reproducing the intervals of 2 secs ($t_{(64)}$ = -2.4, p= .022) and 8 secs ($t_{(64)}$ = -1.9, p= .057).

3.4.2 Time Discrimination

The results of the MANOVA showed a main effect of ADHD ($F_{(3, 104)}$ =2.9, part. η^2 =.077, p =.040), a main effect of age ($F_{(3, 104)}$ =15.7, part. η^2 =.312, p =.000) and a significant interaction of ADHD by age ($F_{(3, 104)}$ =2.8, part. η^2 =.074, p =.045). There was also a trend for the interaction of condition by age ($F_{(3, 104)}$ =2.4, part. η^2 =.066, p =.068). (Table 2)

Univariate tests revealed that the ADHD subjects (both children and adults) produced fewer hits than control subjects ($F_{(1, 106)}$ =7.3, part. η^2 =.064, p =.008), and post-hoc t-tests made clear that this was the case for both conditions with differences of duration longer than 200ms ($t_{(108)}$ = -2.4, p= .018) and shorter than 100ms ($t_{(108)}$ = -2.1, p= .035).

Children compared to adults had fewer hits ($F_{(1, 106)}$ =26.3, part. η^2 =.199, p =.000), increased reaction times ($F_{(1, 106)}$ =21.8, part. η^2 =.171, p =.000) and responded more variably ($F_{(1, 106)}$ =38.3, part. η^2 =.265, p =.000). Post-hoc t-tests showed that children had fewer hits than adults in both duration differences ≥ 200ms ($t_{(108)}$ = -4.0, p= .000) and ≤ 100ms ($t_{(108)}$ = -4.9, p= .000). Age effects were also found for MRT (≥ 200ms: $t_{(108)}$ = 5.6, p= .000; ≤ 100ms: $t_{(108)}$ = 3.2, p= .002) and RT-SD (≥ 200ms: $t_{(108)}$ = 5.6, p= .000; ≤ 100ms: $t_{(108)}$ = 5.6, p= .000).

The interactions of ADHD by age and condition by age were due to univariate effects of MRT (ADHD by age: $F_{(1, 106)}$ =7.7, part. η^2 =.067, p =.007; condition by age: $F_{(1, 106)}$ =3.9, part. η^2 =.035, p =.052) and a trend of RT-SD (only for ADHD by age: $F_{(1, 106)}$ =3.5, part. η^2 =.032, p =.065).

When children and adults were analyzed separately, the ADHD effect remained significant both for children ($F_{(3, 62)}$ =3.4, part. η^2 =.142, p =.023) and for adults ($F_{(3, 40)}$ =3.2, part. η^2 =.195, p =.033). ADHD children continued to differ from control children in the number of hits ($F_{(1, 64)}$ =5.8, part. η^2 =.083, p =.019), whereas adults with ADHD could be discriminated from controls by slower ($F_{(1, 42)}$ =7.6, part. η^2 =.153, p =.009) and more variable response times ($F_{(1, 42)}$ =4.9, part. η^2 =.105, p =.032). Post-hoc t-tests revealed that children with ADHD produced fewer hits than control children, but only in the condition with differences of duration ≥ 200ms ($t_{(64)}$ = 2.7, p= .008). On the other hand, adults with ADHD differed from controls by significantly slower MRT in both conditions (≥ 200ms: $t_{(42)}$ = -3.0, p= .005; ≤ 100ms: $t_{(42)}$ = -2.4, p= .023). In addition, in the condition with differences of duration ≤ 100ms, adults with ADHD showed larger MRT ($t_{(42)}$ = -2.3, p= .028) and a tendency towards fewer hits ($t_{(42)}$ = 2.0, p= .054).

3.4.3 Neuropsychological Tests

Results of neuropsychological tests are shown in Table 3. In the *Alertness* task, neither an ADHD effect nor a significant interaction of ADHD by age was found. There was a significant age effect ($F_{(2, 105)}$ =20.6, part. η^2 =.282, p =.000), a significant interaction for condition by age ($F_{(2, 105)}$ =22.3, part. η^2 =.298, p =.000), and a trend for the interaction of condition by age by ADHD ($F_{(2, 105)}$ =2.7, part. η^2 =.048, p =.074). Univariate tests showed that children responded more slowly and more variably than adults (MRT: $F_{(1, 106)}$ =9.2, part. η^2 =.080, p =.003; RT-SD: $F_{(1, 106)}$ =40.2, part. η^2 =.275, p =.000), and that the condition by age interaction was caused mainly by differences in MRT ($F_{(1, 106)}$ =32.7, part. η^2 =.236, p =.000). The three way interaction trend of condition by age by ADHD, though, was related to differences in RT-SD ($F_{(1, 106)}$ =4.8, part. η^2 =.043, p =.031). Further investigation with post-hoc t-tests revealed that in both conditions children's RT-SD were more variable (with warning: $t_{(108)}$ = 5.4, p= .000, without warning: ($t_{(108)}$ = 5.3, p= .000), and in the condition without warning signal MRT was slower compared to adults ($t_{(108)}$ = 4.2, p= .000).

	Children (N=33/33)				Adults (N=22/22)				Post hoc t-tests [a] N=55/55
	ADHD M(SD)		Controls M(SD)	Post hoc t-tests [b] N=33/33	ADHD M(SD)		Controls M(SD)	Post hoc t-tests [c] N=22/22	
Alertness									
Median of reaction times [ms]									
warning signal	271 (52)		265 (45)	n.s.	246 (45)		258 (62)	n.s.	n.s.
no warning signal	312 (73)		291 (56)	n.s.	252 (49)		254 (52)	n.s.	n.s.
Standard deviation of reaction times (RT-SD) [ms]									
warning signal	92 (43)		91 (60)	n.s.	52 (27)		42 (15)	n.s.	n.s.
no warning signal	92 (53)		68 (32)	*	42 (20)		42 (17)	n.s.	+
Go/Nogo									
Median of reaction times[ms]	450 (93)		478 (86)	n.s.	417 (64)		397 (66)	n.s.	n.s.
RT-SD [ms]	127 (37)		118 (43)	n.s.	86 (35)		65 (16)	*	+
Errors	4.0 (3.5)		3.7 (2.6)	n.s.	0.7 (0.8)		1.0 (1.1)	n.s.	n.s.
CPT									
MRTs for Hits [ms]	460 (91)		451 (79)	n.s.	399 (90)		350 (37)	*	n.s.
RT-SD for Hits [ms]	168 (61)		152 (50)	n.s.	100 (50)		61 (24)	**	*
Hits	36.5 (3.6)		38.2 (3.0)	*	38.5 (1.8)		39.5 (0.7)	*	**
Commission errors	2.4 (2.8)		1.9 (2.6)	n.s.	1.0 (1.6)		0.6 (1.0)	n.s.	n.s.

Post-hoc t-tests: [a] ADHD vs. Controls, N= 55/55, df=108; additional post-hoc tests were separately conducted for [b] children with ADHD vs. controls (N=33/33, df=64) and [c] for adults with ADHD vs. controls (N=22/22, df= 42). n.s.=not significant, p<0.1=+, p<0.05=*, p<0.01=**, p<0.001=***

Table 5: Results of neuropsychological tasks

Although a MANOVA conducted separately for adults revealed a significant interaction of condition by ADHD ($F_{(2, 41)}$ =4.0, part. η^2 =.162, p =.027), post hoc tests did not show significant interactions for any of the parameters analyzed.

In the *Go/Nogo* task a trend for ADHD-related effects ($F_{(3, 104)}$ =2.6, part. η^2 =.070, p =.057), indicated more variable RT-SDs in ADHD subjects than in controls ($F_{1, 106)}$ =4.7, part. η^2 =.043, p =.032). A main effect for age ($F_{(3, 104)}$ =22.1, part. η^2 =.389, p =.000) showed that children responded more slowly ($F_{(1, 106)}$ =13.0, part. η^2 =.109, p =.000), more variably ($F_{(1, 106)}$ =46.2, part. η^2 =.303, p =.000) and committed more errors than adults ($F_{(1, 106)}$ =39.1, part. η^2 =.270, p =.000). When children and adults were analyzed separately, it became evident that the more variable RT-SD in ADHD was due solely to the adults group

(RT-SD .$F_{(1, 42)}$ =6.7, part. η^2 =.137, p =.013), whereas in the children's group there was no significant effect of ADHD.

In the *cued CPT* a significant main effect of ADHD was found ($F_{(4, 103)}$ =2.9, part. η^2 =.100, p =.027). Univariate tests demonstrated that ADHD subjects detected fewer hits ($F_{(1,106)}$ =7.0, part. η^2 =.062, p =.010), responded more variably (RT-SD: $F_{(1, 106)}$ =7.9, part. η^2 =.069, p =.006) and by trend also more slowly ($F_{(1, 106)}$ =3.6, part. η^2 =.033, p =.061) than controls. The effect for age was also significant ($F_{(4, 103)}$ =18.5, part. η^2 =.418, p =.000). Univariate tests showed that children scored fewer hits ($F_{(1, 106)}$ =9.2, part. η^2 =.080, p =.003), committed more errors ($F_{(1, 106)}$ =9.7, part. η^2 =.084, p =.002), and responded more slowly ($F_{(1, 106)}$ =27.7, part. η^2 =.207, p =.000) and variably ($F_{(1, 106)}$ =66.3, part. η^2 =.385, p =.000) than adults. Separate analyses for children and adults resulted in a significant main effect of ADHD in adults ($F_{(4, 39)}$ =3.5, part. η^2 =.266, p =.015), but no significant ADHD effect in the children's group. Affected adults responded with fewer hits ($F_{(1, 43)}$ =5.7, part. η^2 =.120, p =.021), and more slowly ($F_{(1, 43)}$ =5.7, part. η^2 =.120, p =.021) and variably ($F_{(1, 43)}$ =11.1, part. η^2 =.209, p =.002) than controls.

		Time Discrimination				Time Reproduction			
		Hits		Mean RT		Total Mean RT		Total SD	
		Children (N=66)	Adults (N=44)	Children (N=66)	Adults (N=44)	Children (N=66)	Adults (N=44)	Children (N=66)	Adults (N=44)
Alertness	MD no W	-.331**	-0.038	0.095	0.062	0.071	-0.172	0.165	.493**
	MD with W	-.248*	-0.04	0.096	0.073	0.024	-0.047	0.032	.410**
	RT-SD no W	-.351**	-0.072	-0.106	0.169	-0.06	-.279+	0.088	.342*
	RT-SD with W	-0.172	-0.142	0.072	.494**	0.064	-0.124	-0.051	.442**
GoNogo									
	Errors	-0.126	-.349*	-.208+	-0.005	-.291*	-0.078	0.09	0.054
	RT-SD	-0.12	-.514**	0.145	0.203	.243+	-.303*	0.03	.370*
CPT	Hits	.296*	-0.006	-0.05	-0.155	.222+	0.25	-0.138	-0.104
	Comm. Err.	-0.021	-0.001	0.137	.417**	-0.046	-0.005	0.123	0.111
	RT-SD	-.417**	-0.134	.214+	.336*	-0.058	-.262+	.251*	0.236

W = warning signal, MD = median reaction time, SD = standard deviation, p < 0.1 = +, p < 0.05 = *, p < 0.01 = **, p < 0.001 = ***

Table 6: Correlations between time processing and neuropsychological tasks in children and adults

Exploratory Correlational Analysis

In children, the produced interval length from the time reproduction task correlated inversely with errors in the Go/Nogo task (see Table 4). Time discrimination total hits were inversely correlated in the children's group with Alertness MD in both conditions and SD in the conditions without warning, as well as with CPT RT-SD. Time discrimination total hits were positively correlated in children with CPT hits and time discrimination total MRT with SD of the CPT. In the adult group, time reproduction total MRT and total SD were correlated with Go/Nogo SD. In addition, total SD of the time reproduction task showed moderate correlations with all four parameters from the Alertness task. Time discrimination hits in the adult group were inversely correlated with Go/Nogo errors and Go/Nogo SD. MRT of time discrimination was correlated in adults with Alertness SD with warning as well as with commission errors and RT-SD of the CPT.

3.5 Discussion

This study compared neuropsychological performance on time reproduction of seconds and time discrimination of milliseconds in children and adults with ADHD and matched controls. ADHD-related differences in temporal processing were found both in children and adults, indicating that some deficits in this domain persist into adulthood. However, differences in qualitative aspects of ADHD-related deficits in children compared to adults point to a developmental shift of certain key aspects of weaknesses related to temporal processing.

In the time reproduction task, individuals with ADHD were significantly impaired compared to controls, and there was no interaction between ADHD and age effects. However when analyzed separately, children, but not adults with ADHD presented the characteristic underreproduction of time intervals which have been reported in the literature (Barkley, Edwards et al., 2001; McInerney & Kerns, 2003; Rommelse et al., 2007), with an increase of underreproduction in the longer intervals. Adults with ADHD may not be significantly impaired in this type of task because they are able to use compensatory mechanisms in order to overcome their difficulties. The gradual improvement in adults compared to children with ADHD left some residual tendencies for underreproduction, which however no longer discriminated between affected and non-affected adults. This is in contrast to the results of the study by Barkley and co-workers reporting significant underreproduction

in adult ADHD patients (Barkley, Murphy et al., 2001). However, in their study time intervals to be reproduced were considerably longer (up to 60 secs.), so that one might also speculate that adult ADHD deficits may be limited to longer intervals.

In the time discrimination task, different patterns of ADHD-related impairment emerged in children and adults. In children, the ADHD effect was exclusively confined to an increased number of errors. An in-depth-analysis showed that this was due to an increased number of errors in the condition with duration differences of 200 ms or more. This may be related to the greater difficulty of the short duration condition (<100 ms), which presented problems for both groups of children, independent of their ADHD status (floor effect; accuracy of both groups below 62%). In adults, we found the opposite pattern: there was a trend for adults with ADHD to make more errors in the difficult condition (i.e. duration differences <100 ms) than controls, but not in the easier condition (ceiling effect). More importantly, adults with ADHD needed significantly more time than controls to respond in both conditions, whereas reaction time differences did not differentiate between the ADHD and control children in either condition. In this type of task, increased response time is to be interpreted as the additional time needed for comparison processes and decision-making in a cognitively demanding task. This is illustrated by the fact that all subgroups hesitated longer when differences of duration were small. In contrast to tasks tapping response inhibition, the standard deviation of response time did not discriminate the ADHD status in either age group of the present study. Given the different nature of time processing and inhibition tasks this finding is not surprising. Taken all together, maturational improvement in time discrimination is accompanied by a qualitative change in the pattern of ADHD-related impairment and by a shift occurring from error-related towards response time-related deficits. Deviances associated with time discrimination of short durations seem to be stable markers of ADHD, and particularly the impaired discrimination of short durations in ADHD that withstands maturational improvement argues for an enduring vulnerability. This conclusion is in line with recent findings by Himpel et al. (2009), who suggest time discrimination within the milliseconds range as an endophenotype for ADHD. However, one cannot exclude that the results do not only reflect a specific weakness in time perception or internal clock mechanisms in ADHD but are also related to general task difficulty.

None of the standardized neuropsychological test procedures discriminated between the children with ADHD and their controls. This may be explained by the close matching and the high IQ estimates in the children group and is not an unusual finding (see Koschack, Kunert, Derichs, Weniger, & Irle, 2003; Scheres et al., 2004; Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008), though IQ scores may be systematically overestimated here by the algorithm used (Schallberger, 2005). These tests tapping basic processes seem appropriate for correlational analyses, but are probably not specific enough to discriminate between groups of children, especially when the age range and, thus, the range of normal performance is large (Drechsler, Brandeis, Foldenyi, Imhof, & Steinhausen, 2005; Drechsler, Rizzo, & Steinhausen, 2009). Adults with ADHD could be discriminated from controls on the CPT and the Go/Nogo Task. They most notably showed increased mean reaction times and increased variability but also error-related differences in the CPT.

The exploratory correlational analysis showed the expected associations of performance, but only in children: The produced interval length in the time reproduction task was correlated with measures of inhibitory control, i.e. longer and more accurate time reproduction correlated negatively with errors and response time variability of the Go/Nogo task. Also in line with predictions, children's errors in the time discrimination task were correlated with measures of alertness, i.e. simple motor timing, as well as with sustained attention (CPT). The only exception was Alertness SD in the condition with warning which did not correlate with time discrimination MRT. This can be explained by the fact that typically developing children often have to fight the impulse to respond to the warning signal instead of to the target stimulus: for children this task may act as an inhibitory control task (Drechsler et al., 2005). Thus for children, the presumed associations between response inhibition and time reproduction on one side, and state regulation processes and time discrimination on the other side could clearly be demonstrated.

The correlational pattern observed in the adult group was completely different and more complex: the variability of time reproduction was correlated with RT measures of all four Alertness subtasks, especially with reaction time in the more basic motor timing task, but also with SD from the inhibitory control task. At least the latter finding lends support to the hypothesis that in adults with ADHD, variability of response time rather than the number of errors is increased in inhibitory control tasks. This pattern is indicative of deficits in arousal rather than of inhibitory control, as suggested by Halperin et al. (Halperin &

Schulz, 2006; Halperin et al., 2008). Errors in the time discrimination task were related to standard deviation and the number of errors in the inhibitory control task (Go/Nogo), indicating that in adults, errors in the time discrimination task resulted from inhibitory control problems and not from impaired time discrimination as in children. Unexpectedly, adult time discrimination reaction time was associated with commission errors and standard deviation on the CPT and with the alertness condition with warning, i.e. with inhibitory control aspects of tests related to state regulation. This may be interpreted as an association between state regulation and executive aspects of time processing in adults. The result replicates difficulties in disentangling the impact of bottom up versus top down processes on performance in adult ADHD (see King, Colla, Brass, Heuser, & von Cramon, 2007) suggesting that attentional deficits may contribute to executive deficits (Bekker et al., 2005).

3.6 Limitations

Adults with ADHD were selected among the parents of children with ADHD if they scored above the cut-offs on two self-rating scales including a retrospective assessment for ADHD symptoms. It may be argued that at least some of these adult ADHD participants only showed subclinical impairment. Probably, they were also better integrated into society than a clinical adult ADHD clientele in need for professional help. On the other hand, this sample might be more representative of the true developmental course of ADHD in the adult population than clinically referred ADHD patients. Furthermore, the presence of neuropsychological endophenotypes should not depend on the current ADHD status.

3.7 Conclusion

This is the first study which directly compared time processing performance in ADHD affected children and adults. ADHD-related deficits in time processing persisted from childhood into adulthood, but seemed to change their form of appearance during development. There is some evidence that in childhood ADHD effects due to executive function deficits on one side and more basal time processing problems on the other side coexist and that they can be relatively well distinguished. In the adult sample, manifestations of time processing deficits seemed to be related more clearly to basic processes, such as arousal or time perception in the milliseconds range, but they could not be completely divided from

executive functions and inhibitory control which seem to interact on a more subtle level in adults than in children.

4 General Discussion

ADHD-related differences in temporal processing were found both in children and adults, indicating that some deficits in this domain persist into adulthood. However, differences in qualitative aspects of ADHD-related deficits in children compared to adults indicate that certain key aspects of weaknesses related to temporal processing undergo a developmental shift.

4.1 Neurophysiological Markers of Time Processing and Inhibition

ERP markers of time processing and inhibition as well as performance data reflected both age and ADHD status.

Regarding development, adults performed better than children, which is in line with a large body of evidence on developmental improvements of attention and inhibition (Casey, Giedd, & Thomas, 2000; Jonkman, Lansbergen, & Stauder, 2003). Furthermore, topographies of Nogo P300 and CNV showed an anterior shift from childhood to adulthood.

Regarding ADHD status, performance was poorer, and Cue CNV and Nogo P300 were weaker in ADHD children and adults compared to their matched controls.

Closer separate analyses of children and adults revealed interesting aspects: in children, concerning CPT performance, no multivariate significance of the ADHD-effect could be found despite ADHD children omitting more hits (in the Standard CPT) and committing more errors (in the Flanker CPT) than control children. It seems that the two task versions may have measured partly different performance deficits, as the less demanding Standard CPT suggested more attentional lapses, whereas the more difficult Flanker CPT revealed inhibitory weaknesses in ADHD children compared to control children, and task related variance may thus have obscured an overall ADHD effect.

Adults with ADHD were slower and more variable in their mean reaction times than control adults in both task versions, but differences were more pronounced in the easier Standard CPT, with ADHD adults additionally omitting more hits only in the Standard CPT. This is the same pattern as in children, with the only difference that ADHD children showed more commission errors, whereas in adults, these inhibition lapses were replaced by state regulation weaknesses. The CPT, especially the Flanker CPT, might have been too

difficult for children, independent of their ADHD status, and thus ADHD deficits were found only as tendencies. In adults, ADHD-related deficits were elicited more clearly, with greater mean reaction times and MRT variability dominating over commission and omission errors contrary to children's performance. These overt performance data show clearly that problems with response inhibition are not relevant in adults anymore. Instead, they show weaknesses in state regulation. Furthermore, most unexpectedly, ADHD adults showed greater weaknesses in the Standard CPT than in the Flanker CPT compared to control adults. Comparison between the Flanker and Standard CPT showed that for ADHD adults, the Standard version seemed not to be easier than the Flanker CPT as their performance was about the same in both tasks. One explanation for this outcome could be that, for adults with ADHD, the easier task was not demanding and challenging enough and therefore they were kind of "bored" and not able to generate the required attentional effort, which could be another hint at weaknesses in state regulation.

Concerning CNV, our results show that topographies differed between children and adults, suggesting a developmental change of ADHD-related impairments. While brain regions associated with CNV, such as dorsolateral prefrontal cortex and anterior cingulate cortex (Gomez, Marco, & Grau, 2003; Lutcke et al., 2008) develop along with improving attentional functions after childhood (Jonkman et al., 2003), the CNV differences between healthy adults and adults with ADHD persist. Since the CNV is a composite of several generators and brain areas involved (Macar, 2004), it is possible that this continued CNV amplitude reduction in ADHD adults reflects the influence of subcortical rather than cortical regions, and is related to aspects of pure time processing associated with the CNV rather than to executive aspects.

The more anterior CNV in adults than in children was evident in maps and tomographies, and is in line with previous developmental CNV findings that left frontocentral late CNV negativity only appeared after age 11 in adolescents which has been interpreted to reflect the relatively late development of brain areas involved in response preparation (Bender, Weisbrod, Bornfleth, Resch, & Oelkers-Ax, 2005). The children's more anterior CNV in the Flanker CPT compared to the easier Standard CPT resembles a shift towards a more adult-like pattern. As the children in the present study were at an age where these brain areas might just start to develop, the more challenging flanker CPT may have

prompted them to engage a more “adult” pathway, resulting in a more adult-like, anterior CNV topography.

Concerning Nogo-P300, both children and adults showed ADHD-related differences. In children, these differences were more posteriorly, whereas in adults, they were more anteriorly located. Both maps and tomographies suggested that this shift is due to the lack of ACC activation in children whose posterior activity still dominated. Control and ADHD children were differentiated more clearly in the Standard CPT than in the obviously too difficult Flanker CPT, but the difference is not as strong as in adults. ADHD adults were differentiated from the control adults much more in the Flanker CPT than in the Standard CPT.

Taken together, our results show a developmental shift of ADHD deficits from inhibitory deficits in children to problems in state regulation in adults. Furthermore, taken apart the weaker performance of ADHD adults in the Standard CPT compared to the Flanker CPT and the children’s (both controls and ADHD) more adult like CNV in the Flanker CPT compared to the Standard CPT, the flanker version discriminated better between adults with and without ADHD, whereas the easier Standard CPT generally reflects the differences between ADHD and control children clearer.

4.2 Neuropsychological Markers of Time Processing

Children demonstrated problems with both the time reproduction and the time discrimination tasks. As the former task requires also inhibitory functions and correlations were found with tasks measuring response inhibition, whereas in the latter task which requires more basal time processing in the milliseconds range, correlations could be found with tasks measuring alertness and sustained attention. In children, executive function deficits were still present due to not yet fully developed frontal cortex and coexisted with more basal subcortical deficits like weak state regulation and impaired temporal processing.

In adults with ADHD, underreproductions in the time reproduction task were still present, but they did not discriminate them in a statistically significant way from controls. Other studies report significant underreproductions in adults with ADHD (Barkley, Murphy et al., 2001), but these adults were considerably younger than the present adults sample and had to reproduce intervals which were up to 50 seconds longer than in the task used here.

Obviously, adults with ADHD were unimpaired in the reproduction of intervals up to 8 seconds or were able to use compensatory mechanisms in order to overcome their difficulties. The results are compatible with a gradual improvement observed in adults compared to children with ADHD, with some remaining residual tendencies that do no longer discriminate between affected and non-affected adults.

The time discrimination task seemed to be more suitable for testing time processing in adults, as this task is focusing more on unconscious processes like state regulation and basal temporal processing that are not or not to the same extend mediated by the frontal cortex. Thus, executive functions cannot act directly as compensatory mechanisms. Here, enhanced reaction time and slightly more errors in ADHD adults indicate that they indeed had problems with certain aspects of temporal processing. However, compensatory inhibitory and attentional processes might interact in a more complex way with basal timing and state regulation processes in adults than in children.

Temporal processing seems to be a stable marker or endophenotype in ADHD, although its behavioural / observable expression is different in children and adults. Time reproduction tasks can well demonstrate time processing weaknesses in children with ADHD, but not anymore in adults, unless the task is made more difficult as shown by Barkley et al. (Barkley, Murphy et al., 2001). It is therefore probable, that problems due to executive function deficits can be found in time reproduction tasks in adults with ADHD, provided that the task is demanding enough. According to its level of difficulty, the time discrimination task seems to dissociate children's from adults' performances: the easier trials with duration differences of more than 200 ms are well suited to show differences between ADHD and control children, but for adults, they seem to be too easy to elicit any ADHD-related differences (ceiling effect). In the more difficult condition of this task with duration differences shorter than 100 ms, though, the reverse pattern emerges: too difficult for children independently of their ADHD status (floor effect), but well suited for adults in order to demonstrate weaknesses in time processing in ADHD adults.

Taken all together, maturational improvement is accompanied by a qualitative change in the pattern of ADHD-related impairment and by a shift occurring from error-related towards response time-related deficits. Deviances associated with time discrimination seem to be stable markers of ADHD, and particularly the impaired discrimination of short durations in ADHD argues for an enduring vulnerability. This conclusion is in line with recent find-

ings by Himpel el al. (2009), who suggest time discrimination within the milliseconds range as an endophenotype of ADHD. However, one cannot exclude that the results do not only reflect a specific weakness in time perception or internal clock mechanisms in ADHD but are also related to general task difficulty.

4.3 Relating the Neuropsychological and Neurophysiological Findings

The CNV has already been described as reflecting an on-line marker of time processing without motor confounds. In terms of specific hypothesis, it is difficult to relate this CNV either entirely to an „automatic“ or exclusively to a „cognitive“ system. Considering the interval length of 1650ms (as determined by the interstimulus interval in the cued CPT), and considering that CNV generators include frontal cortex areas like the SMA and the ACC, it clearly involves cognitive executive processes mediated at least partly by cortical structures. Thus from this point of view, the CNV should be more closely related to the time reproduction task used here than to the time discrimination task. On the other hand, the CNV is at least partly controlled (although not generated) by subcortical structures. In addition, it seems relatively unconfounded from general attentional, inhibitory, or motor aspects of task processing which are captured by other (P300 type) components in different phases of the cued CPT. Accordingly, the temporal expectancy component (evaluating when the Stimulus 2 will appear) could well be related to the pulse accumulator of the “automatic” system. As a consequence, one expects correlations between CNV measures and both time processing tasks.

Table 1 which illustrates these correlations supports these conclusions.

		CNV Standard			CNV Flanker			Nogo Standard			Nogo Flanker		
		Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
Children													
Time dis-crimination	Hits	ns	ns	-.334**	.249*	ns	-.304*	ns	.282*	.309*	ns	.305*	ns
	RT	ns	ns	ns	ns	ns	ns	.286*	ns	ns	.326**	ns	ns
Time re-production	RT	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	SD	ns	ns	ns	ns	.236+	ns	ns	ns	ns	ns	ns	ns
Adults													
Time dis-crimination	Hits	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	RT	ns	.289+	ns	ns	ns	ns	ns	ns	ns	ns	-.260+	ns
Time re-production	RT	ns	-.253+	ns	ns	ns	ns	.312*	ns	ns	.330*	.265+	ns
	SD	ns	.305*	ns	ns	ns	.290+	ns	ns	ns	ns	ns	ns

Table 7: Correlations between CNV / Nogo P300 and neuropsychological time processing tasks

4.4 General Conclusion

Although temporal processing deficits have been found to a certain degree in this work, and have also been reported in children, adolescents and young adults with ADHD by others (Barkley, Edwards et al., 2001; Barkley et al., 1997; Barkley, Murphy et al., 2001), determining them as endophenotypes has to be done with caution and with taking into account that time perception is a construct containing widespread functions that are, in turn, associated in different ways with ADHD. Compensatory mechanisms acquired during brain development as shown by Halperin et al. (2006) may cover core ADHD-deficits and make them less evident. As such, and according to our results, the observable deficits in temporal processing in children may be due to problems both in executive functions like inhibition and attentional control and to basal time processing. In adults on the other hand, they could be due to insufficient arousal and state regulation and basal time processing that could, in turn, disturb more or less intact executive functions. Based on our neurophysiological and neuropsychological investigations, internal pace maker and arousal allocation could therefore be interpreted as stable markers or endophenotypes in ADHD. Both internal pace maker and arousal allocation are crucial components of time processing, but two important aspects have to be taken into account: 1) they are differentially strongly involved in different aspects of time processing. The existing theories and investigations in the field of time processing lead to the conclusion that they mainly play an important role in temporal processing of time aspects in the milliseconds range, where uncontrolled and more automatic processes are involved. 2) While dealing with time related tasks, children and adults may use pace maker abilities and arousal allocation in different ways, because on the one hand, these two functions are differentially far developed and on the other hand, because more and possibly different compensatory strategies are available to adults than to children.

How should endophenotypes as “stable markers” be interpreted, if they change their phenotypic appearance throughout development? In our case, time processing has to be divided in several subfunctions, among which only a certain aspect can be considered as endophenotype in ADHD, which is more basal aspects of time processing, without attentional or motor confounds. Furthermore, in order to research for the same or stable markers in children and adults with ADHD (or any other disease that persists but changes certain aspects during development), tasks have to be well adapted to the individuals’ cognitive

state, i.e. differ in their level of difficulty while qualitatively still measuring the same aspect. Otherwise, the different outcomes in children and adults with regard to developmentally caused overlaps of underlying stable deficits have to be interpreted with caution, because the equivalence of child and adults samples with ADHD is weak and uncertainty exists in the question to which degree individual tests may measure the same construct in children and adults (Halperin & Schulz, 2006).

Regarding this, neuropsychological procedures, in combination with neurophysiological strategies that make covert cognitive processes measurable, are most promising.

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Curriculum Vitae

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